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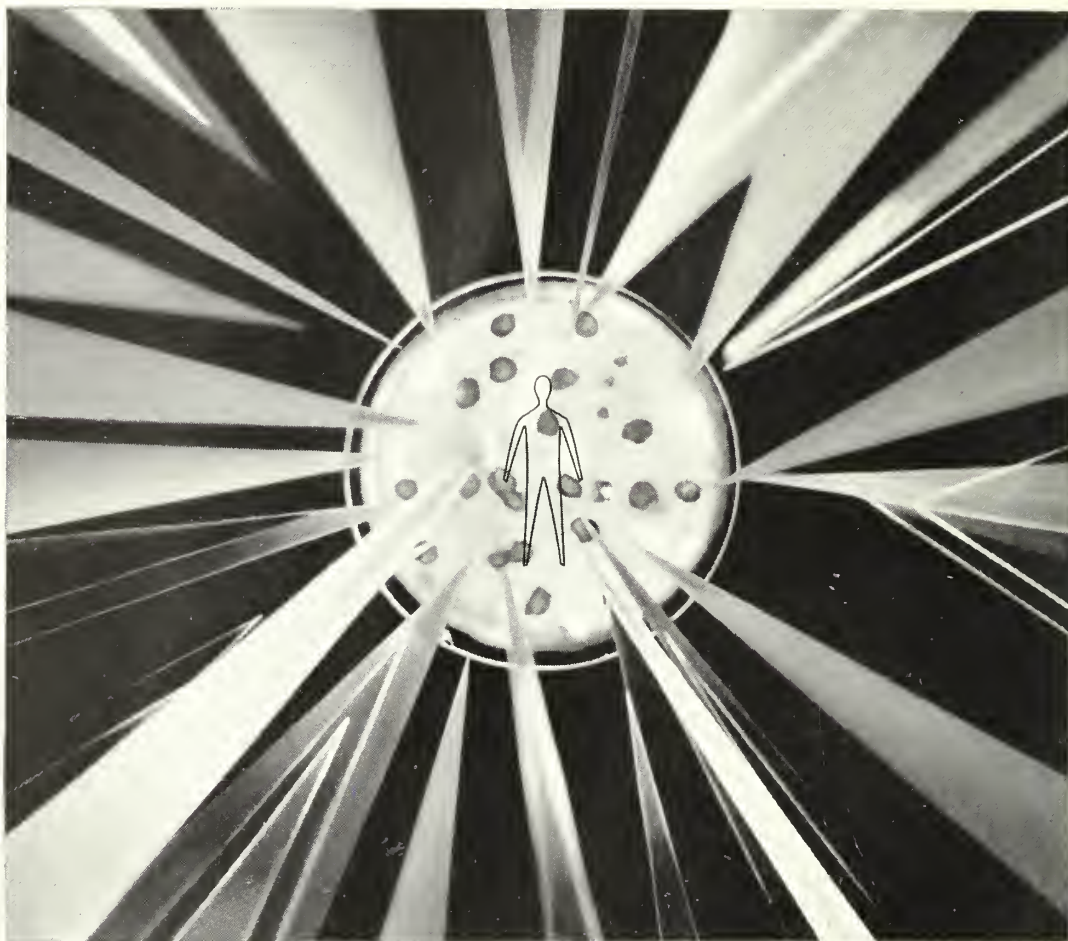
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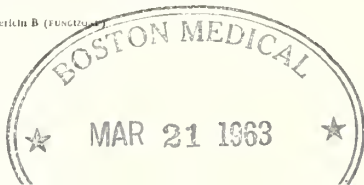
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Cancer of the Large Bowel

With Special Reference to the Colon, Including Consideration of the Second-Look Procedure

OWEN H. WANGENSTEEN, M.D.

Minneapolis, Minnesota

SINCE 1940, the vital statistics of the United States have consistently shown that cancer of the large bowel, including both colon and rectum, takes a larger toll of life than cancer in any other organ. The reason for this circumstance is that cancer of the large bowel affects both sexes frequently.

In 1957, the last year for which a complete record of vital statistics¹ is available, there were 37,523 deaths from cancer of the large bowel in this country, of which number 26,689 occurred in the colon and the remaining 10,834, in the rectum; 45 per cent of deaths from cancer of the colon occurred in the male, whereas 56 per cent of the deaths from cancer of the rectum occurred in the male.

In the same year, there were 21,522 deaths from gastric cancer, of which 62 per cent occurred in the male.

The vital statistics for 1957 list 22,459 deaths from cancer of the breast in the female; 8,597 deaths from cancer of the cervix; 1,253 from cancer of the uterus and 4,923 deaths from unspecified malignancies of the uterus; 14,296 deaths from cancer of the prostate; and 14,617 deaths from cancer of the lung and bronchus, of which 11,732 occurred in the male. There were 16,159

additional cases of tumors of the lung, unspecified as to whether primary or secondary, of which number 12,545 occurred in the male.

Incomplete figures for 1958 parallel this recital of deaths from cancer of the various organ systems. This brief narration suffices to indicate what the more frequent fatal malignancies are. Cancer of the large bowel leads the list. It also serves to indicate how important the problem of early detection is. Many a surgeon's lament is that he has spent his life on the wrong side of the wood pile. He yearns to get over to the green or early cases but does not know how to do it. Techniques which would make it possible to recognize cancer in its early stages regularly would do much to make cancer a less formidable foe.

THE UNIVERSITY OF MINNESOTA'S EXPERIENCE IN CANCER DETECTION

What have been the few areas of special accomplishment in cancer detection? Dr. Donald Shanon, one of a succession of competent surgeons in my department, who guided the destinies of our cancer detection center during its twelve years of operation, found there were 3 areas in which detection was effective. One of these was a source of great surprise to everyone in our clinic—the breast; the other 2 were no surprise—the cervix and the rectum.

The breast is a subcutaneous organ. Even so, cancer of the breast is detected late far too often.

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More women die of cancer of the breast than from cancer of any other single organ. A tremendous impress could be made upon the cancer problem if deaths from cancer of the breast could be erased or greatly lessened. Cancer of the cervix as a cause of death appears to be dwindling. A report from the Metropolitan Life Insurance Company^{2,3} a few years ago suggested a definite decrease in the mortality (27 per cent) of its women industrial policyholders from cancer of the female reproductive organs—a circumstance occasioned largely, probably, by the value of the Papanicolaou smear in the detection of cancer of the cervix. Among approximately 11,000 patients, about half of whom were women, Jensen, Shahon, and Wangenstein⁴ found 30 patients with cancer of the breast in a survey of the University Hospital Cancer Detection Center experience. Apart from 1 patient who failed to return for observation over a period of two years and who ultimately reported with an advanced breast cancer, the other 29 patients found to have breast cancer survived. We have not been able to duplicate this accomplishment in our own hospital experience, in which group cancer is detected on the basis of a palpable lump, usually discovered by the patient. It will interest you to know that 70 per cent of these 30 women failed to detect the lump in their breast through the agency of self-examination. This fact suggests very definitely that an annual routine examination by competent and interested observers is far superior to self-examination in the detection of breast cancer.

The other area in which cancer detection proved useful and helpful was the rectum. Inasmuch as cancer of the rectum is frequent in both men and women, an annual proctoscopic examination must be a part of the cancer detection examination. In this group of 11,000 patients—in many of whom adenomatous polyps were discovered on proctoscopic examination—no patient developed rectal cancer while under observation, suggesting that an annual proctoscopic examination can be very helpful in the control of one of the frequent cancers in both men and women.

Proctoscopic examination is, as some of you may have had occasion to learn, not a very pleasant experience. Women will come for speculum examination of the vagina more readily than they will submit to proctoscopic examination. We have found that hypnotherapy can be employed to persuade refractory patients to accept such examinations. As yet, we have lost no proctoscopes—but our endoscopists tell us a sigmoidoscopic examination is a simpler and far less traumatic experience for objectors under hypno-

therapy. In other words, it is possible to transmit suggestions in the hypnotic state which patients reject when awake. The American language stands in great need of a word to connote the transition from rejection to acceptance. Time and work are the catalysts which effect this conversion in most of life's trials. Every man can identify many such examples in his own experience.

Apart from these 3 areas—the cervix, breast, and rectum—there were no other areas in which cancer detection played a significant role. Occult cancer of the colon was recognized in some patients but missed in others. Many gastric polyps were found and an occasional early gastric cancer. We are all awaiting anxiously the development of screening tests which will simplify the problem of recognition of cancer. When the time comes that surgeons get over to the other side of the woodpile, where the green cases are piling in day by day, whether it concerns the rectum, colon, breast, stomach, or lung, the advantage to the patient of having his cancer identified early will make a tremendous difference in the outlook.

The experience of the University of Minnesota Cancer Detection Center suggests definitely that special clinics should be established in many areas of our country for earlier detection of breast cancer. The Minnesota Division of the American Cancer Society accepted this suggestion and has already followed through with one such examination in the Crookston area.⁵ The response was startling. In consequence, a number of women were found harboring silent breast cancer, recognized sufficiently early to provide reasonable promise of cure. If the experience of the University of Minnesota Cancer Detection Center and that of the Crookston survey are borne out in other areas of our country, it is quite apparent that cancer of the breast would presently cease to be the first cause of death from cancer among women.

CANCER OF THE COLON

Approximately 75 per cent of cancers of the large bowel, that is, the colon and rectum, are within reach of a 25-cm. sigmoidoscope. The American Cystoscope Company is engaged in the manufacture of a flexible instrument like the flexible gastroscope—an instrument which may extend the visual reach of the endoscopist. As was indicated earlier, proctoscopy is superior to roentgen examination in the detection of early lesions. The shortcoming of endoscopic procedures in the large bowel is distance. If roentgenography were as efficient in the detection of early colic

tumors as is the proctoscope in the terminal reaches of the large bowel, the large annual toll from colic and rectal cancer would not be what it is today. Reliable diagnostic methods for early tumors would certainly make an indelible and lasting impact upon the mortality rate from cancer of the colon.

Antecedents of colic and rectal cancer. For most cancers which affect man, save skin cancer, the antecedents are not known. In the colon and rectum, on the contrary, it is generally believed that the adenomatous polyp is the usual precursor. Though some controversy has hedged about this point recently, there is fairly general agreement among most students of the problem that a definite relationship does exist between adenomatous polyps and the eventual development of cancer in the large bowel or rectum. It appears to be well documented that colic or rectal polyps in the young may disappear spontaneously. This latter condition is not to be confused with familial polyposis, which frequently makes its appearance in adolescence and progresses steadily until cancer supervenes.

Near-total or total colectomy for colic cancer. For a number of years, I have championed total or near-total colectomy as the primary operation for all colic cancers distal to the hepatic flexure.^{6,7} Several patients who have had antecedent operations for the excision of a previous colic cancer have said to me following total or near total colectomy, "Why was this not done the first time?" I submit it is a good and proper question. Whereas all surgeons are not prepared to accept total or near-total colectomy as the operation of choice for colic cancer in 1960, or even in 1961, I believe that, by 1965, more will do so. Since 1944, this operation in standard-risk patients has been the conventional operation for patients with colic cancer distal to the hepatic flexure (figure 1A). It is surprising how often an unexpected cancer is found in the excised colon in an area which is not reached by the conventional segmental colectomy. Moreover, silent adenomatous polyps, which probably eventuate in cancer, are encountered frequently when near or total colectomy is done for colic cancer.

For cancer of the colon proximal to the hepatic flexure, in which instances excision of the terminal ileum is necessary to catch the lymphatic drainage area in the operation, excision of all the distal colon would deprive the patient of his ileum. The water-wringer of the bowel is the terminal ileum and right half of the colon. Patients in whom the entire colon but no ileum is removed do not have persistent diarrhea. The best operation I know for ardent constipation is

excision of 25 to 30 cm. of terminal ileum, together with the right half of the colon. In fact, I have done the operation twice under this indication. Moreover, many a patient with cancer in the cecum or ascending colon has been at least as appreciative of being rid of constipation through the operation as being cured of the cancer.

The technic of anastomosis employed in this clinic for a quarter of a century has been and is a closed operation (figure 1B). We conventionally give no antibiotics. Our best experience was in the years 1941 to 1943, when, over a two-year period, 61 consecutive patients with colon cancer were operated upon by the closed technic, with only one death.⁶ We have not done that well, may I say, in intervening years, with increased experience, use of antibiotics, and other adjuvant aids which have come meanwhile. All the antibiotics in all the pharmacies of Galveston, and in your hospitals too, cannot afford the patient the same protection as a well-performed closed anastomosis in which there is no spillage. On completion of the anastomosis, the tube shown in figure 1C is passed up beyond the anastomosis from below. After the catheter guide is withdrawn, the 30 cc. balloon is distended with a quantity of water which adjusts comfortably to the luminal diameter of the bowel.^{7a}

An adequate lymph node dissection is a mandatory part of a well-performed operation for colic cancer. For a right-sided cancer, one removes the lymph node-bearing area along the vena cava, carrying the dissection up to the inferior border of the pancreas. Such lymph node removal has done a good deal, I believe, to improve ultimate survival in colic cancer. For cancer of the left half of the colon, a para-aortic dissection is done, carrying the dissection to the left renal vein. For cancers of the transverse colon, both paravena cava and para-aortic lymph node removals are carried out.

The primary operative mortality for colectomy in this clinic continues to be between 4 and 5 per cent. For Dukes' Group A lesions, the five-year survival rate has been in the area of 80 per cent; for Dukes' B lesions, about 65 per cent; and for Dukes' C lesions, with lymph node involvement, only 45 per cent.^{11,12}

THE SECOND-LOOK PROGRAM

It was the large disparity in accomplishment between lymph node-negative and lymph node-positive cancers that suggested the need for the second-look procedure.⁷ There are many lessons yet to be learned through use of second-look operations. One might believe that all worth know-

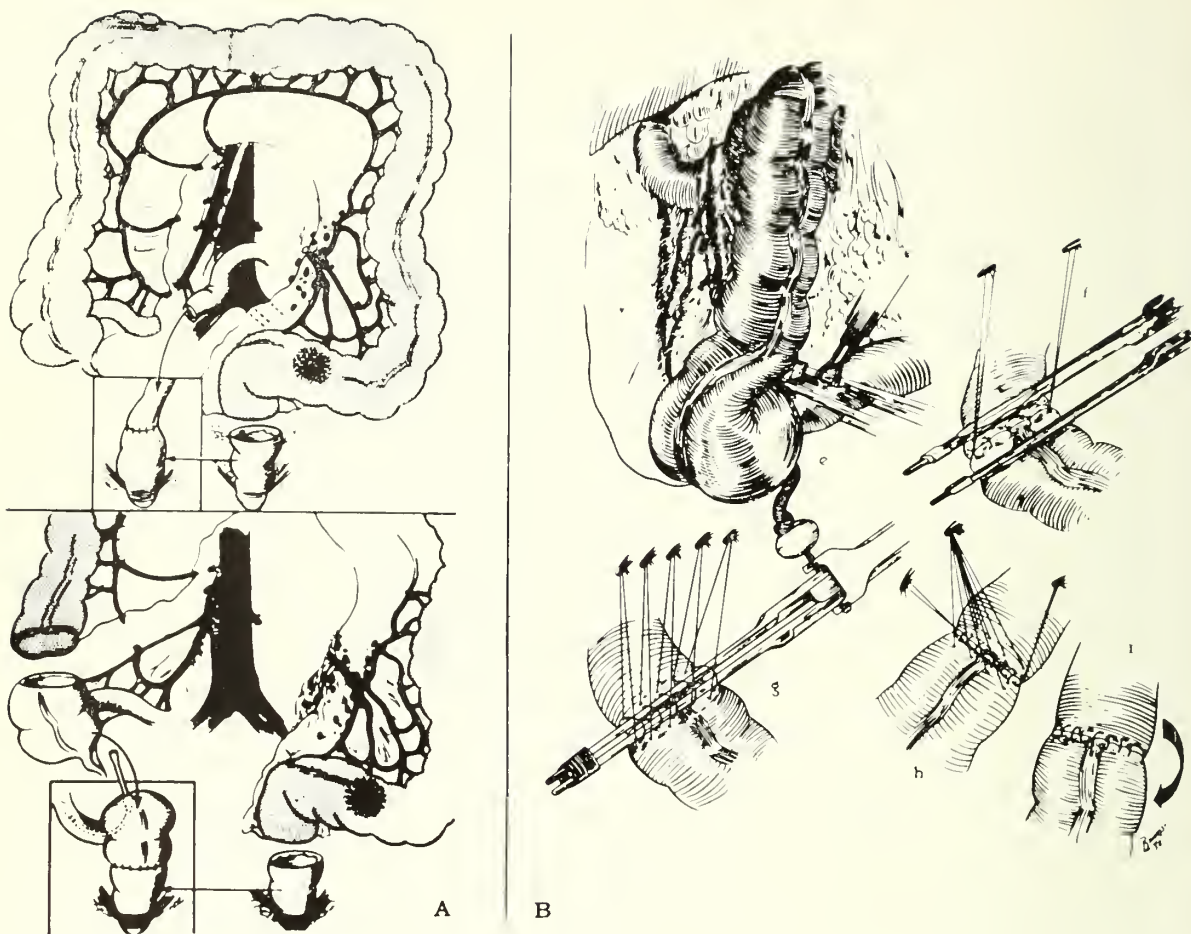
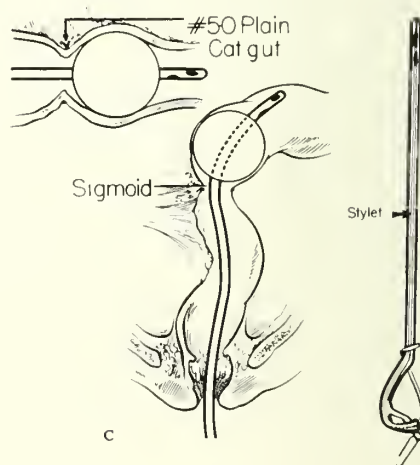


Fig. 1. (A) The operation for cancer of the colon. The extent of excision of the colon. In the upper illustration, the entire colon is excised with an ileoproctostomy. Below is shown anastomosis of the ascending colon to the rectum. In both operations, an adequate lymph node dissection accompanies the procedure. For cancers distal to the hepatic flexure, these operations are not attended by persistent diarrhea. If it becomes necessary to excise a fairly long segment of ileum—more than 10 cm. in length—such extended removal of the colon with sacrifice of ileum may be followed by transient diarrhea. Extended excision of the colon can be accomplished with the same operative risk in standard-risk patients as segmental resection. Frequently, another silent cancer is found in the excised colon, and it is not unusual to remove simultaneously many polyps quite removed from the primary lesion. (B) Closed anastomosis, which has been used continuously in this clinic in colon resection since 1938. Before the anterior row of sutures is tied, an Allis forceps is applied to the midsection of both distal and proximal segments of the anastomosis; the untied sutures are pulled laterally, thus permitting inspection of the posterior suture line from within. If the mucosal apposition is not as perfect as it should be, placement of 3 to 5 fine chromic catgut sutures suffices to provide assurances on this score. The assistant pulls up the silk sutures, while the surgeon changes his gloves, because his fingers have been in contact with mucosa in the placement of these stitches. (C) Sketch illustrating placement at operation of No. 30 Foley catheter into sigmoid colon. The use of a catheter guide makes it a very simple procedure to pass the tube up through the rectum without encountering difficulty from Houston's valves. The balloon (30 cc.) is inflated with water to a size comfortably adjusted to the diameter of the bowel. A No. 5(00000) plain catgut stitch is passed through the mesentery and is tied gently without compressing the bowel inferior to the balloon.



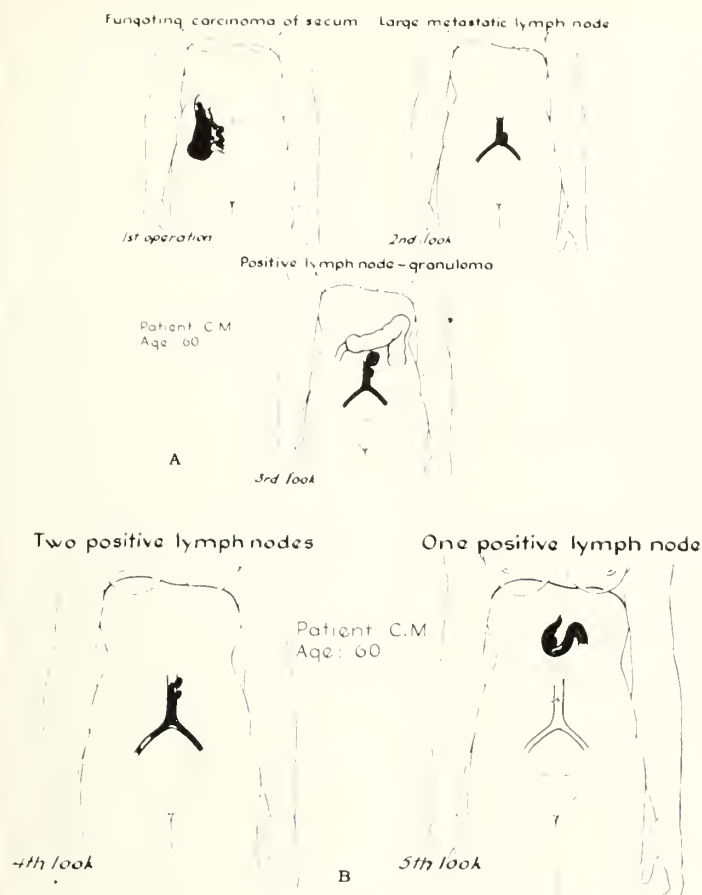


Fig. 2. (A) The second-look procedure in the instance of Mrs. C. McK. Operations were done at six- to seven-month intervals. At the first operation (1948), large, obvious cancerous lymph nodes in the ileocecal angle were uncovered. The cancer was also adherent to the anterior abdominal wall, necessitating sacrifice of a portion thereof. Succeeding illustrations indicate the findings at the second- and third-look procedures. (B) Situation at fourth and fifth looks. A final and sixth look was negative for cancer. (C) Patient approximately ten years after last operation. Mrs. C. McK. survived for more than twelve years and died in the University Hospital of pneumonia, consequent upon a hypertensive cerebrovascular accident. Complete autopsy failed to disclose any residual evidence of cancer. She had been very active during the intervening years.

ing has been learned in an experience of more than a decade with the procedure, but undoubtedly there are indications for the second-look operation other than lymph node-positive cancers. Many Dukes' B cancers in which the lesion extends to or through the serosa should have reoperation. Moreover, patients who are converted to a cancer-free status, who initially had a good deal of lymph node involvement, probably should be explored again about two years after a negative look. I recently did this in a patient with a cancer of the ovary, with a surprise finding of 2 cancerous lymph nodes in 2 widely separated areas. Two years hence, I propose having another look.

In figure 11A is depicted the series of operative procedures on my first second-look patient, Mrs. C. McK. On her sixth look, no residual evi-

dence of cancer was found. The patient survived for more than twelve years and died of pneumonia as a complication of a hypertensive cerebrovascular accident. A complete autopsy was performed. No residual cancer was found. Fortunately, with the aid of the Minnesota Division of the American Cancer Society and with help from the Damon Runyon Cancer Fund, the patient was spared any expense relating to the many second-look procedures. No period of hospital stay was longer than seven days; it would be nice indeed if convalescence from all second-look procedures was so smooth. When it was my privilege to tell her, after the sixth look, that she was cancer-free, her stoicism broke for the first time, and she revealed understandable traces of a need for an emotional outlet in tears.

Obviously, the second-look program makes it

mandatory to tell patients they have cancer. I have yet to surprise a patient by telling him he has cancer. He knew it before. Many a time a patient will ask me following operation, "Doctor, what did you find?" Invariably, I reply by saying: "You know, of course, you have a cancer." Before I can amplify on what was done, the patient often says something like the following—"How glad I am you told me. Now I can discuss it with my husband. He does not know that I know I have a cancer." In my experience,⁸ these words lie very near the surface on patients' lips and await the wanted and needed help from the surgeon to prompt their immediate release and articulation, which is followed, I have observed, with a feeling of great relief on the part of the patient.

Now, a few remarks concerning the second look for cancer of the stomach. Three such patients in whom residual cancer was found at the

first relook procedure have gone beyond five years. Two of these again, after long intervals, exhibited evidences of residuals. One still lives twelve years after the first operation, free from cancer. A recent study of our second-look failures by my colleague, Dr. Victor Gilbertsen,⁹ indicates a definite prolongation of life by the procedure, even though the patient may ultimately succumb to the cancer (table 1). The same prolongation, also, as compared with palliative procedures, was observed for the "failure" group of second-look operations undertaken for cancer of the rectum (table 2).

If carcinosis is present on many areas of the small intestine, the cancer is already out of hand. However, large areas of peritoncum, including that of the diaphragm, the pelvis, and lateral peritoneal gutters, together with all the omentum, can be sacrificed with impunity, as can long segments of the colon and portions of the small intestine, if need be. Often, these are long and strenuous operations, taking the greater portion of the day. Yet these can be rewarding experiences, not alone for the patient but for the surgeon, too.

ANCILLARY SOCIOLOGIC ASPECTS OF THE
SURGEON'S ROLE

A favorite question of mine to patients whom I see in the outpatient clinic who are found to have cancer is "How old do you want to live to be?"¹⁰ The answer, though couched by patients in different language, in substance is always the same. Patients, no matter who they are or what station in life they occupy, say, in effect, "As long as the weather is fair and the company reasonably pleasant, do whatever you can to keep me alive. I want to continue living." Life is still worthwhile to old people.

The surgeon has a responsibility to see to it that the old person who has been rescued by an operation for cancer has a friend to whom he can speak occasionally. One of the important causes of death from old age is loss of one's friends. The life of many an old man, I have observed, can be converted from one of utter desolation to one of enjoyment and radiant happiness by finding him a nearby crony with whom he can spend a friendly hour or two each day. For one such patient, with the help of an interested daughter-in-law and a sympathetic social worker, I found a succession of checker players. The patient, now in his upper 80's, still survives and has found life, once an almost unbearable burden, to be full of contentment and satisfaction. How pleasant and rewarding such experiences are for the surgeon, too.

TABLE 1

SCHEMATIC SKETCH INDICATING THE PROLONGATION
OF LIFE ACHIEVED IN SECOND-LOOK FAILURES
FOR CANCER OF THE STOMACH

Survival time	Excisions for cure Dukes' C lesions			Palliative excision cases %
	Over-all group %	Succumbed to recurrent cancer		
		Over-all group %	Second-look cases %	
1 year	65	57	84	10
2 years	35	18	41	2
3 years	28	11	25	0
4 years	25	7	19	0
5 years	19	0	3	0

TABLE 2

SCHEMATIC SKETCH INDICATING THE PROLONGATION
OF LIFE ACHIEVED IN SECOND-LOOK FAILURES
FOR CANCER OF THE RECTUM

Survival time	Excisions for cure —Dukes' C lesions—				
	Succumbed to —recurrent cancer—			Palliative excision cases 12 mo.° (%)	Colostomy only cases 5 mo.° (%)
	Over-all group 24 mo.° (%)	Over-all group 21 mo.° (%)	Second- look cases 26 mo.° (%)		
6 mo.	85	83	100	73	42
1 yr.	70	67	92.5	49	21
18 mo.	59.5	55.5	81.5	—	—
2 yr.	49	44	63	20	5
3 yr.	36	30	37	9	2
4 yr.	27	20	18.5	7	—
5 yr.	21	13	7	2	—
6 yr.	17	9	4	2	—
7 yr.	14.5	6	—	—	—

°Median survival



Fig. 3. (A) A large retroperitoneal fibrolipomyxosarcoma. This patient had twice been explored previously in other hospitals; attempts at excision of the tumor had been abandoned. Excision demanded sacrifice of the greater portion of the colon and approximately 100 cm. of the ileum. A temporary ligature was placed on the lower abdominal aorta below the renal vessels early in the procedure to minimize hemorrhage from the pelvis—an expedient which has proved very helpful in the extirpation of many large abdominal tumors. Subsequent reentries were made periodically at six- to eight-month intervals. The sixth operation proved to be negative for residual sarcoma. (B) The patient, Mr. G. C., several years after the excision. He is well and has been continuously employed up until his retirement recently. His only complaint is diarrhea, occasioned by the extensive excision of colon and ileum made mandatory by removal of the tumor at the first procedure.

Two areas, in addition to the colon, in which it has been possible to make long-time conversions to a cancer-free state through the agency of the second-look procedure are (1) the large retroperitoneal sarcoma of the fibrolipomyxomatous variety (figure 3), today more often called rhabdomyosarcoma, and (2) cancer of the ovary.

Among large retroperitoneal sarcomas,¹³ 2 of 13 patients have been converted to a cancer-free state through the agency of the second-look procedure. The first of these necessitated 6 operations; the other took 4 procedures. A third patient was free from demonstrable malignancy for many years, when pulmonary metastases came into evidence.

Cancer of the ovary has proved an especially hopeful field for the second-look venture.¹⁴ Of 22 patients, 3 have been converted by multiple reentries of the abdomen. The spread of the malignancy in many of these patients at the initial procedure has been great. Ovarian cancer transplants itself onto the peritoneum, much of which can be sacrificed. It is involvement of large areas of the peritoneum covering the small intestine that thwarts the efforts of the surgeon employing

the second-look procedure to halt the progress of cancer of the ovary.

SUMMARY

Cancer of the large bowel, including the colon and rectum, takes a large toll of life. In fact, more lives are lost annually in the United States from cancer of the large bowel than from cancer of any other organ. Moreover, cancer of the large bowel is a frequent neoplasm in both sexes.

There is no uniform agreement concerning the antecedents of cancer of the colon and rectum. Most experienced students of the problem concede that the adenomatous polyp is a frequent precursor. Failure of cancer to develop in a large number of patients observed in the Cancer Detection Center at the University of Minnesota over a period of many years in whom adenomatous polyps were found and fulgurated in the rectum, thus thwarting development of cancer, suggests a definite relationship between adenomatous polyps and rectal cancer. Findings of our Cancer Detection Center suggest, too, that an annual physical examination of the breast will recognize cancer in this subcutaneous organ

early enough to afford fairly uniform promise of success.

Acceptance of an annual proctoscopic examination for all men and women over 40 years could come to have a telling effect upon the mortality of cancer of the rectum and the lower segment of the bowel within the reach of the sigmoidoscope. More precise radiographic techniques need to be developed for the colon which will match the greater accuracy and efficiency of endoscopic examinations. Endoscopic examination of the colon up to the splenic flexure may become a reality with the development of a flexible endoscope with provision for direct forward vision.

Near or total colectomy is the operation of choice for cancer of the colon. It can be done at about the same risk as segmental colectomy (4 to 5 per cent). For cancers above 10 cm. or more from the anus, anterior excision affords about the same promise of cure as does the more radical abdominoperineal excision. For the majority of cancers less than 10 cm. from the anus, the standard-risk patient must accept the abdominoperineal operation in order to reap the maximal promise of cure. A radical lymph node dissection is a matter of important primary concern in this initial operation, as is wide excision of the cancer.

Obstruction of the colon from cancer, accompanied by great distention, must, in most instances, be managed by a decompressive operation. In most instances, a transverse colostomy, performed on the transverse colon through a transverse abdominal incision placed directly over the transverse colon, is the operation of choice. As a prelude to primary excision, a preliminary cleansing enema is the best preparation and has long been the principle emphasized in this clinic for the preparation of patients for operations upon the colon.

The cure rate for cancer of the colon and rectum is contingent in large measure upon the status of the lesion at the time of operation. A cancer of the colon confined to the mucosa (Dukes' A), when radically excised, is accompanied by a cure rate of approximately 80 per cent, with lesser accomplishments for Dukes' B and C lesions. Inasmuch as a more complete operation for cancer can be executed in the colon than in the rectum, the cure rates for cancer of the colon, in the main, are correspondingly better than those achieved for the rectum.

The second-look procedure has proved to be

an operation of real worth in cancer of the colon. The five-year conversion rate is in the area of 10 per cent. Other areas in which the second-look operation has been especially helpful in effecting a salvage of life, otherwise unobtainable, are retroperitoneal fibrolipomyxosarcomas (rhabdomyosarcomas) and cancer of the ovary. Even when the second-look operation has failed to establish a cancer free state, it would appear that definite prolongation of life is often achieved.

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Depression

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DEPRESSION in its various forms is one of the common afflictions of mankind. It is a frequent visitor to the offices of all physicians. The textbook symptoms are depression or sadness (whence the name), hopelessness ("the future looks black") and feelings of helplessness, irritability, a tendency to self-blame, difficulty in concentration, indecision, loss of interest in usual activities, a frequent wonder if life is worth going on with, and, often, changing somatic symptoms ranging from headache to nausea. Loss of interest in sexual affairs is the rule and is one of the first symptoms to appear and one of the last to reappear, but this is simply one of many losses of interest. Loss of interest in food, with resultant weight loss, plus fatigue and pallor often cause the physician to think first of organic diseases such as cancer, tuberculosis, or anemia. The so-called masked depression usually describes the situation wherein the patient's symptoms in the somatic field overshadow emotional complaints such as sadness, irritability, and so on. Restlessness ("I can't sit still") is often an annoying symptom.

EVALUATION

Someone once said that if the ten best minds in the world gathered around a table to concoct the worst experience a human being could go through, it would be depression, and there is a great deal of truth in this. The suffering of such a patient is intense—so intense that death often appears the preferable route of solution—and the possibility of suicide must be kept in mind constantly while treating depressed persons. While almost all depressed people will think of death and suicide, this does not mean that it always represents a serious risk but rather is one which

must be evaluated. My own procedure of evaluation goes something like this:

M.D.: Knowing that you are suffering from a depression, I presume that every now and then you are hit by thoughts that life isn't worth the effort.

Patient: Yes, doctor, that's right. This morning I found myself wishing I would get cancer and die.

M.D.: Every depressed person has these feelings. Do they ever hit you so hard that you become afraid you might do something to yourself?

(At this juncture there are two general alternatives, shown in the descriptive chart.)

Alternative A

Patient: Yes, I am having a good many thoughts of how I might kill myself. Maybe I'd be too big a coward though. I'm really a pretty sad sack, aren't I?

M.D.: You are definitely ill and should be in the hospital so that we can study you completely and decide on the best treatment for you. Also, I am certain you will feel more comfortable in the hospital in a protected setting. I would like you to come into the hospital today. This probably seems like a big decision, but it's one I would like to make for you.

Patient: Are you going to give me shock treatment?

M.D.: This might well be the best treatment for you, but I'd rather reach a decision on what is the best approach after studying you for a few days in the hospital. Incidentally, you have my promise that no treatment will be started without discussing it with you. If we decide upon shock therapy, I will need your written permission. You don't need to worry about surprises or doing anything without your knowledge.

Alternative B

Patient: Oh, no, I didn't mean that. I've had a few wonders about it but it's not a real problem. No, I haven't worried much about that.

M.D.: I just wanted to ask because I wouldn't want to take any chances with you.

Patient: I don't think you need to worry about that.

M.D.: Very well. One thing let me mention, however. I am well aware how hard it is to go through a depression, and should it ever occur that you do get crowded on this score, I want you to call me. I don't care whether it is 3:00 A.M. or if I am at a dinner party at the President's house. I want you to call me. Can we make a gentleman's agreement on this?

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Patient: OK. You want me to call you if it should turn out that sometime I get that depressed?

M.D.: That is correct. So much for this. Now let's go on . . .

In other words, I am inclined to accept the patient's own evaluation of suicidal risk unless I have clear-cut evidence to the contrary. For example, if I have a patient who has made a suicidal attempt before seeing me but then passes it off lightly or claims that he took all those sleeping pills "by accident," I am understandably skeptical about his statements in this regard. In my experience, however, the evaluation of the patient himself can be trusted 99 per cent of the time.

PHYSICIAN'S ATTITUDE

I do not need to point out that such a discussion as that just outlined must rest on a satisfactory doctor-patient relationship. Many people, upon recovery from a depression, will comment how helpful it was to know that the doctor wanted him to call if he got into trouble with suicidal thoughts. The physician is as near as the telephone, and this type of reassurance seems very helpful, particularly when the patient wakes up during the reaches of the night when the rest of the world is asleep. It has not been common in my experience for such a patient to call on this score. On the few occasions when patients have done so, I have regarded it as a medical emergency and have asked the patient to meet me at once at the office regardless of time of day or night, with hospitalization as the usual outcome.

The attitude of the physician toward the depressed patient is tremendously important. If the physician truly regards depression as an illness, his actions follow more or less naturally, since he can keep it in the same frame of reference as he does any illness, whether it be pneumonia, depression, or appendicitis. The person suffering with depression has always gone through a long period when he tells no one about it, suffers alone, and keeps hoping against hope that when he wakes up the next morning he will feel well again. He tells himself constantly to "buck up," "snap out of it," "forget it," "I should get a hobby," "it's all in my head," and attempts of this kind. He can be relied upon to have said to himself, "If I had any guts, I could pull myself together." He inevitably finds that none of this bootstrap pulling helps. He then goes on to confide his distress to his wife or a close friend, and, because they may not understand depression any better than he does, more often than not he runs into the same type of advice—"buck up," "snap out of it," and so forth.

The patient by this time is only too well aware that no help is to be found here.

The point I am getting at is this: If now, after these experiences, he finally goes to the physician with his trouble only again to bump into the same set of attitudes ("you need a vacation," "you should make yourself get out and play golf," and so on), the patient is now truly at the end of his rope. Where else can he go to try to find someone who really understands him and what he is trying to say? This is an extremely frustrating and disheartening experience for someone who is already frustrated and disheartened.

When the physician handles him like any other sick person—takes a careful history, examines him physically, gets indicated laboratory work (one must not forget that emotional illness does not immunize against coincidental organic disease), and treats his sickness with dignity and understanding—the depressed person realizes that help is on the way and that he has someone on whom he can depend.

It is usually helpful to tell the patient the classical symptoms of the illness to help him to realize that the doctor understands him. For example, although the patient may not have mentioned it, I may, in reciting the usual symptoms, say something to this effect: "Most people going through this have a great deal of indecision. It often seems as if it takes as much energy to decide to comb one's hair as to buy a new house. All decisions come to be major ones, with the person stuck on dead center." Usually, the patient will amplify his symptoms at this point, perhaps saying, as one patient did around Christmastime, "Before this appointment with you, I was at D's (local store) trying to buy presents for my grandchildren. I simply couldn't decide and gave up in disgust without getting them anything. I called my husband at his office and told him I was a sorry mess not even to be able to get presents for my own grandchildren. I was bawling over the phone. That's why my eyes are so red."

FAMILY ATTITUDES

All emotional illness produces difficulty and rupture in family relations, and depression is no exception. One interesting aspect in this area relates to the fact that a depressed person, if not too sick, can pull himself together for short periods of time when a social setting requires it. For example, although the woman may be quite depressed and spending most of her time immobilized and crying, if a salesman comes to

call, she will quickly put on a false front, act cheerful and almost gay for ten or fifteen minutes, only to go down in a heap when he leaves. Her husband sees her constantly depressed and out of sorts when he is with her but does not fail to notice what happens when the minister or someone else comes in. He will often develop a good deal of resentment about this, thinking, "If she can do this for the preacher, why in heaven can't she do it for me?" What he does not realize is that she could not continue to do this for anyone for any length of time. This is a phenomenon that must be kept in mind by the physician with respect to himself, since the depressed person will put his best foot forward on his initial contacts with the doctor. It is almost the rule to hear the family or referring physician describe the patient as very depressed, only to see little sign of it on the first visit. I have my own rule of thumb about this—I multiply by four the symptoms I see on the initial interview with the depressed patient.

Family, nurses, and hospital personnel also need to be aware of this, since, for the first day or so, the patient usually will do his best to hide his illness, only to show it in its true magnitude as he gets to know the hospital personnel and to feel somewhat at home in the hospital setting. This creates the illusion that the hospital has suddenly made the patient much worse, and family and staff personnel can easily become upset by this turn of events. In actuality, all it means is that the patient either can no longer maintain the false front or feels more at home and hence has less necessity to conceal his symptoms. Beyond a point of severity of illness, the patient cannot put on this false face regardless of the circumstances.

It is characteristic of depression to show a diurnal variation—the morning is usually the worse time of day, with the symptoms letting up to some extent as the day wears on.

THERAPY

In the extreme grades of depression, electroshock therapy is still the backbone of treatment. The trend today is more and more to treat the patient under thiopental sodium anesthesia and succinylcholine chloride, and, unless the psychiatrist has undertaken special training, this should be done by an anesthesiologist. While this increases the expense, it permits the anesthesiologist to maintain an open airway throughout the treatment and hence to avoid exposing the patient to hypoxia. It also permits utilizing electroshock in

seriously depressed patients with cardiovascular complications who otherwise might be denied the benefits of the therapy.

A number of new antidepressant drugs have appeared recently on the market, although there has not yet been time for an adequate clinical evaluation of them. Reports in the literature seem to indicate an unpredictable effect, some authors reporting that they do nothing and others enthusiastic about one or several of them. Because there is so little that can be said as yet about them and because there are no data which indicate that one has advantages over another, one must suspend judgment until more knowledge is at hand. In general, a reasonable approach to the new antidepressant drugs might be as follows: if the patient is not suicidal and is to be handled as an outpatient, pick out one or another of the drugs and give it a therapeutic trial for a minimum of two weeks. If there is little or no change for the better after two weeks, try one of the others. The physician must, of course, be aware of the side effects of each drug he uses. If none of the newer antidepressant drugs helps and the patient remains about as sick as ever, electroshock therapy may then be considered. This decision must be made by a psychiatrist.

Regardless of what drugs or treatment is used, the physician should keep in mind the great therapeutic effect that he himself has on the depressed patient. An attitude of objective understanding, a willingness to be of help, patience when things do not move as rapidly as one might wish, and equanimity when the patient is scared are potent psychotherapeutic tools. The general physician should not hesitate to discuss personal problems with his depressed patient but probably should stay in the area of current events. The psychiatrist may or may not elect to probe and to try to relate the depression to emotional factors which hurt the patient many years before. In talking about personal problems, the nonpsychiatrist should keep in mind that the depressed person tends to look at himself through black glasses and that he may distort previous events, for example, adolescent masturbation, into terrible evils. Avoid taking this kind of material at face value. The patient will often be amused by such distortions upon recovery.

The prognosis for most depressions is good—by spontaneous recovery, psychotherapy, drugs, electroshock, or combinations of these approaches.

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Arteriovenous Fistula of the Lung

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THERE are a number of terms under which this clinicopathologic entity, arteriovenous fistula of the lung, is described in literature, such as pulmonary arteriovenous aneurysm, cavernous hemangioma, pulmonary telangiectasis, congenital arteriovenous varix, and multiple pulmonary hemangiomas. On pathologic grounds, however, the most logical name for this condition seems to be arteriovenous fistula.

In 1897, Churton¹ described multiple pulmonary arteriovenous fistulae in the lungs at post-mortem examination. In 1918, G. D. Wilkins² found, at necropsy of a 1-year-old girl who died of pulmonary hemorrhage, 1 fistula in the left lung and 2 on the right. In 1923, De Lange and De Vries-Robles,³ in a postmortem examination of a 2-month-old infant, found 2 pulmonary hemangiomas in the lungs. Bowers,⁴ in 1936, reported a case of a newborn baby who died from pulmonary hemorrhage caused by rupture of pulmonary hemangiomas into the pleural cavity, and, in 1938, Rhodes⁵ described a patient with pulmonary arteriovenous fistula who died from rupture into the bronchus. Smith and Horton⁶ in 1939 diagnosed a cyanotic case as an arteriovenous fistula with polycythemia, clubbing of the fingers, and shadows in the right lung. In 1942, Hepburn and Dauphinee⁷ described a case of arteriovenous fistula. Shenstone⁸ performed pneumonectomy for this lesion for the first time, with disappearance of dyspnea, cyanosis, polycythemia, and clubbing of the fingers after operation. Since then, about 400 cases of arteriovenous fistula of the lung have been reported.

PATHOLOGY

Macroscopic. The arteriovenous fistula is a congenital defect of the pulmonary capillary vascular bed which may be caused by either lack or failure of fusion or by formation of septa between the arterial and venous channels, with hypoplasia of the blood vessels, which then rupture and cause bleeding. It is usually seen as a thin round sac, generally lying peripherally be-

neath the pleura. It varies in shape, most often seen as an irregularly round, lobulated mass, and in size, ranging from very small to quite large, occupying the entire lobe. The fistula may be situated in any part of the lung but is usually in the lower lobe, may be single or multiple, and unilateral or bilateral, and may be associated with hemangiomatous malformation in other systems of the body.

Arterial and venous drainage vary. In most cases, the arterial blood comes from one of the pulmonary arterics, but it may also come from systemic circulation from the bronchial or intercostal artery or from the aberrant artery; mostly, it comes from the thoracic aorta, as described by Watson.⁹ The venous blood is drained into the main vein of the same lobe in which the arteriovenous fistula is situated but may also drain into the vein of the adjacent lobe; venous drainage of the whole lung may be involved.

Microscopic sections. The microscopic sections show that the intima of the arterial vessels is normal, that there is very little muscle in the wall, and that the amount of elastic tissue varies, there being none in many cases. The histologic picture of the vein is normal.

Pathologic physiology. The arteriovenous fistula is usually a congenital right-to-left extracardiac shunt, and, as a result, unoxygenated blood bypasses the alveolar capillary bed and returns to systemic circulation. The clinical picture of the patient depends on the size of the shunt, the number of arteriovenous fistulae, the source of the arterial blood supply (systemic or pulmonary), and the amount of unoxygenated blood which returns to systemic circulation. When the arterial blood supply to the arteriovenous fistula comes from the systemic circulation, clinical manifestations of anoxemia are absent but the pressure within the arteriovenous fistula is increased and there is greater danger of rupture of the fistula. As time passes, degenerative changes take place within the arteriovenous fistula. Large cavities form, which may cause the fistula to rupture, resulting in hemorrhage. The amount of blood passing through the shunt was estimated by Maier¹⁰ to be 58 per cent

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and, by Lindgren,¹¹ to be from 25 to 30 per cent. In one case of Baker and Trounce,¹² blood passage through the shunt was 80 per cent, and, in another, cardiac output was 12 liters per minute.

Laboratory findings. There is a rise in the blood volume, caused by increase of red cells, which may reach 12,000,000, with hemoglobin up to 25 gm., without concomitant increase of the plasma volume. The blood volume may rise to about 12 liters and arterial oxygen saturation may be less than 70 per cent (usually 63 to 84 per cent). There is also a greater carbon dioxide content in the arterial blood. Polycythemia also increases the viscosity of the blood, with a greater incidence of thrombosis, and, despite increased volume and viscosity of blood, there is no rise in blood pressure. Coagulation, bleeding time, and prothrombin concentration are within normal limits. Circulation time, as measured by sodium dehydrochlorate, is usually normal but may be shorter or prolonged. Total and differential white cell count and platelets are normal. The electrocardiogram may be normal or show right axis deviation.

Radiologic findings. Routine chest films usually show abnormal shadows varying in size from small to large and occupying a part or the whole lobe of the lung. They are usually round or oval, with regular or irregular walls and defined borders, and are connected to the hilum with linear markings which are caused by blood vessels. Tomograms will show these features clearly, as well as other fistulae and calcification, undetectable on the conventional films.

The fistula may be either single or multiple and may be situated in any part of the lung but most often is found in the lower and middle lobes. On x-ray screening, it may pulsate, with the size growing by the Valsalva maneuver and reducing by the Müller maneuver, according to the status of the intrathoracic pressure. Selective angiocardiograms are essential before operation to determine the presence of a number of fistulae and their origin in the lung and the vascular arrangement of the blood supply and drainage. However, any arteriovenous fistula in which the blood is clotted will not be outlined by the dye, and often, when there are many multiple minute fistulae, angiocardiograms will fail to reveal their presence.

Clinical manifestations. Arteriovenous fistulae may be discovered in persons of any age. The fistula is usually a congenital lesion, either asymptomatic or overlooked in early life and is usually diagnosed in the third or fourth decade of life. Those found in the later age have nearly

always been present for many years. Patients may be divided into two groups—the asymptomatic and the symptomatic. Asymptomatic persons are either picked up on mass radiography or on some other routine examination of the chest.

The symptomatic group is distinguished by 3 principal features—dyspnea, cyanosis, and clubbing of the fingers. The clinical picture of cyanosis depends on the size of the shunt and the amount of blood which bypasses the pulmonary circulation. The cyanosis appears, as has been stated, if the shunt is large and more than 30 per cent of the blood bypasses the pulmonary circulation and is caused by anoxemia. Anoxemia causes polycythemia, which increases the blood volume and the viscosity of the blood. Cyanosis may be absent or may develop at a later stage. When it does occur it may be severe, as in congenital heart disease. Dyspnea, another cardinal symptom of arteriovenous fistula, is caused by low arterial oxygen saturation and higher CO₂ content, which stimulates the respiratory center. Clubbing of the fingers and toes is caused by cyanosis and vasodilation.

Patients often complain of epistaxis and coughing up of blood. According to some authors, this occurs for the first time in adult life. The epistaxis, caused by telangiectases in the nose, may result in anemia if there is severe loss of blood. Symptomatic patients are anemic rather than plethoric.

Cerebral symptoms, such as headache, dizziness, vertigo, weakness, and convulsions, may be caused by cerebral anoxemia and polycythemia, which leads to increased viscosity of the blood and thus to cerebral thrombosis or to cerebral angiomas.

Examination of the lung is usually negative, but, in few patients, there may be impaired percussion. A murmur, if present, is either continuous or systolic and is heard over the area of the lung overlying the arteriovenous fistula. The heart shadows in the chest film are within normal limits, and the electrocardiograms are usually normal but may show right axis deviation. It is very likely that all these cases are associated with hereditary telangiectasis. According to some authors, 40 per cent of the cases of arteriovenous fistula have capillary hemangioma of the skin and mucous membrane. B. T. Le Roux,¹³ in his series of 6 cases, found 3 patients with mitral stenosis as well.

COMPLICATIONS

Rupture of arteriovenous fistulae, infection, and cerebral lesion are the main complications. De-

pending upon whether the arteriovenous fistula is in the center or the periphery of the lung, it may rupture into the bronchus or into the pleural cavity, producing hemothorax. Brink¹⁴ described 2 patients with telangiectasis of the lungs, one of whom had hemoptysis, hepatic angioma, and hematuria. The other forms of bleeding, such as epistaxis, hematemesis, and hematuria, occurring in patients with arteriovenous fistulae, are caused by related Rendu-Osler-Weber disease.

The common infectious complication is a cerebral abscess, and cases of bacterial endarteritis also have been described in the literature. In 1953, F. H. Stevenson¹⁵ described a case of arteriovenous fistula infected with *Staphylococcus aureus* which was successfully treated by penicillin and Aureomycin. Meachant and Scott,¹⁶ in 1958, reported a case of congenital pulmonary arteriovenous fistula complicated by brain abscess; both lesions were successfully treated. According to them, the brain abscess was caused by imperfect oxygenation of the blood, which renders the cerebral tissue more susceptible; infarction or infected embolus producing infarct may also play a role in the development of this lesion.

INCIDENCE

In the majority of cases, the arteriovenous fistula was present at birth, being overlooked or asymptomatic at that time, but most commonly is found in middle-aged persons. The lesion is said to occur more often in men than in women. According to Muri,¹⁷ the ratio of male to female is 3 to 1. Steinberg and McClenahan¹⁸ found this not to be the case: of 9 patients, 6 were females and 3 males. In our group of 3 cases, all were middle-aged men. According to Sloan and Cooley,¹⁹ in 15,000 consecutive autopsies at the Johns Hopkins Hospital, only 3 cases of arteriovenous fistula of the lung were found. The arteriovenous fistula is a manifestation of hereditary telangiectasis and, in most cases, is a part of general disease even if it may be the only symptom noted. In patients who have only arteriovenous fistulae in the lung, it usually happens that other members of the family in the same or another generation show some aspect of hereditary hemorrhagic telangiectasis.

A family history of either epistaxis or "spots" of mucous membrane on the lips and mouth is found in about 40 per cent of the cases of arteriovenous fistula.

CASE HISTORIES

In this series of 3 cases, there was a classical case of Rendu-Osler-Weber disease. The patient's father and 1 of 3 sisters had "spots" on the lips.

This patient had hemangiomas on the lips and tongue and arteriovenous fistula in both lungs. Vertebral angiograms showed cerebral vascular malformations which were responsible for his neurologic symptoms of giddiness, fainting attacks, and unsteady gait. The 2 other patients of this series, found by mass radiography, were asymptomatic. All 3 had a systolic murmur best heard in the area overlying the arteriovenous fistula, and all had a round shadow with characteristic vascular markings connecting this lesion with the hilum.

Case 1. H. P., a 52-year-old man, was picked up by mass radiography in 1958, with a shadow in the left upper lobe, and was admitted to hospital. His father and 1 of his 3 sisters had had "spots" on the lips and were bleeders.

His general admission was good on admission. He had been cyanotic since the age of 4, had been giddy as long as he could remember, and, in later years, had had frequent epistaxis and fainting attacks. He was dyspneic on exertion and his gait was unsteady.

On examination, there was well-marked telangiectasis on the face and, to some extent, on the tongue and buccal mucous membrane (figure 1). The jugular venous pressure was normal, and the heart was not enlarged. There was a continuous murmur, which was best heard in the second left interspace. Pulse was regular and blood pressure was 170/100 mm. Hg. The cranial nerves were normal. There was cerebellar ataxia. Knee reflexes were exaggerated and plantar response normal.

Blood count revealed: hemoglobin, 118 per cent; stabs, 3 per cent; neutrophils, 79 per cent; monocytes, 5 per cent; lymphocytes, 12 per cent; prothrombin concentration, 100 per cent; basophils, 5 per cent; red blood cells, 4.8 million per cubic millimeter; platelets, 215,000; and white blood cells, 12,000. Urine was normal.

Posteroanterior and lateral chest films on admission showed complex rounded opacities in the anterior segment of the left upper lobe (figure 2). Tomograms made June 10, 1958, showed that this rounded lesion seen in the films was connected by the blood vessels with the hilum (figure 3). Selective angiocardiograms showed arteriovenous fistulae in the left and right upper lobes. Samples of blood taken from the left pulmonary artery

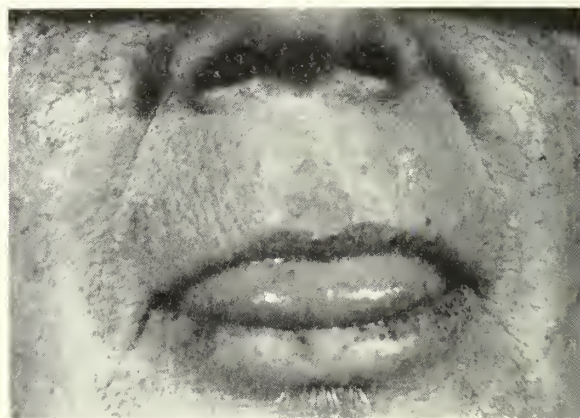


Fig. 1. Telangiectasis on face, tongue, and lips



Fig. 2. Posteroanterior and lateral roentgenograms on admission show rounded opacities in anterior segment of left upper lobe.

had 79 per cent oxygen saturation and from the right femoral artery, 94 per cent oxygen saturation.

It was believed that cerebral angioma might account for the continued symptoms of giddiness and unsteadiness of gait. The patient was therefore referred to a neurologist for a second opinion before decision regarding thoracotomy was made. The neurologist found impairment of upward conjugate movement and slight impairment of the position sense in the big toes. He considered that there might be intracranial hemangioma; vertebral angiograms showed "a small vascular malformation filling from the left superior cerebellar artery. There were also one or two doubtful regions but this was the only definite telangiectasis" (figure 4). In view of these findings, no attempt was made to operate on the pulmonary lesion.

Case 2. D. W., a 38-year-old man, was noted on mass radiography to have an opacity in the left lung base and was admitted to hospital for investigation.

On admission on October 19, 1958, his general condition was good. He complained of a slight cough with whitish sputum, which was never blood-stained, and dyspnea, which had increased in the six months before admission.

On examination, the chest was clinically clear, jugular venous pressure was normal, and heart was not enlarged. There was a harsh systolic murmur in the sixth left interspace in the axillary line, more pronounced on inspiration. Pulse was regular, of the water-hammer type, and blood pressure was 140/70. The blood count showed hemoglobin, 122 per cent; white blood cells, 8,900; neutrophils, 73 per cent; stabs, 2 per cent; lymphocytes, 15

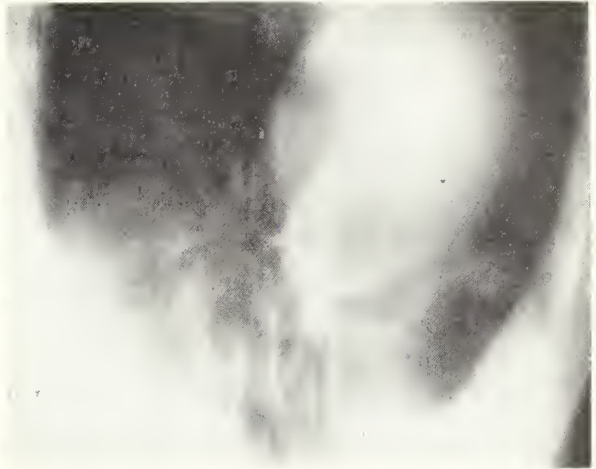


Fig. 3. Planigrams show rounded lesion of figure 2 connected by blood vessels with the hilum.

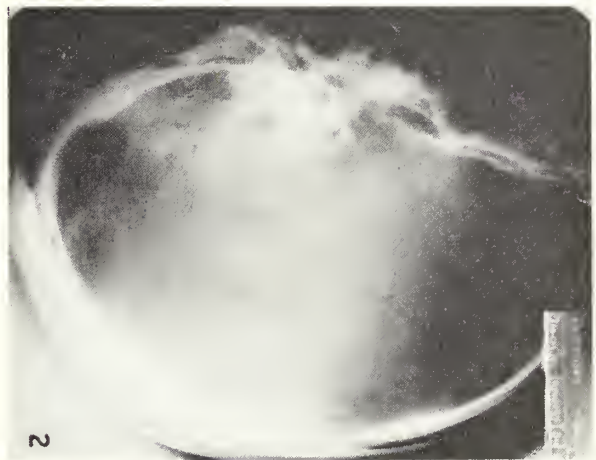
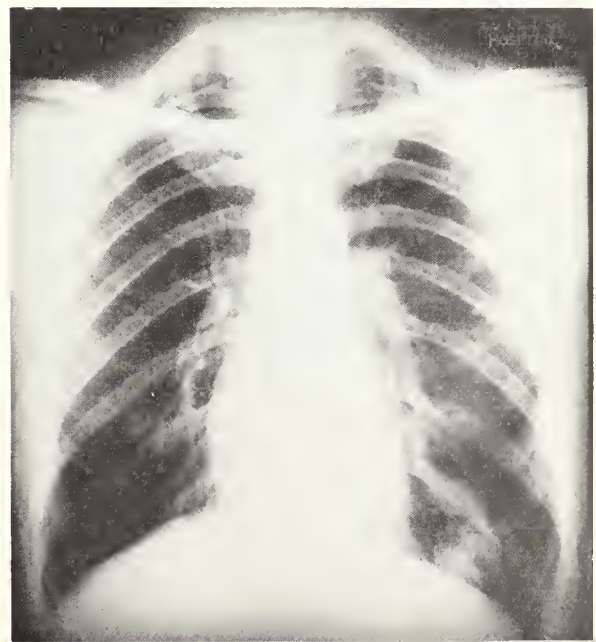


Fig. 4. Vertebral angiograms show a small vascular malformation filling from the left superior cerebellar artery. There are also 2 doubtful regions, but this is the only definite telangiectasis.

Fig. 5. Chest film shows an irregular shadow in the left lower lobe connected by linear markings to the hilum.



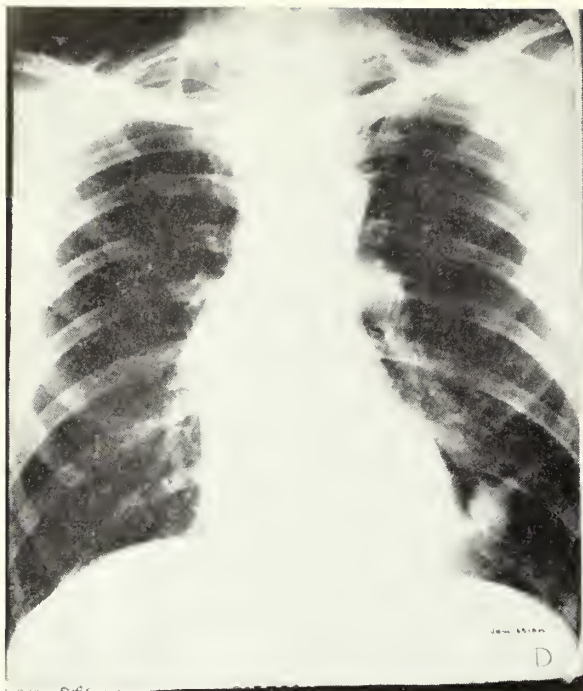


Fig. 6. Chest film shows an irregular density in the left lower lobe connected by vascular shadows to the left hilum.



Fig. 7. Resected specimen shows an arteriovenous fistula, about the size of a grape, with its blood vessels.

per cent; monocytes, 7 per cent; and eosinophils, 2 per cent. Roentgenograms of the chest indicated an irregular shadow in the left lower lobe connected by linear markings to the hilum (figure 5). Selective angiocardiograms revealed arteriovenous aneurysm of the left lower lobe and quite a large shunt with a large venous component. No other aneurysm could be seen in either lung.

Segmental resection of the anterior basal segment of the left lower lobe was carried out on November 4, 1958. In this segment was a collection of thin-walled, tortuous blood vessels, the largest of which formed grape-like projections on the surface. No thrill was palpable over this area, and the pressure was low in these vessels. The main artery to the lower lobe was larger than normal and that to the anterior basal segment was extremely small and thin-walled. The vein draining this segment was also about double the normal size. The anterior basal segment was removed.

Case 3. A 62-year-old man was noted on mass radiography in 1954 to have a shadow in the left lower zone and was admitted to hospital for investigation and treatment in August 1957. His general condition was good. On clinical examination, he had no symptoms or abnormal signs in any system of the body. Blood count and urine were normal.

Roentgenograms of the chest on admission showed an irregular density in the left lower zone connected by vascular shadows to the left hilum. Tomograms showed that the lesion was in the left lower lobe and was connected to the hilum by vascular shadows (figure 6).

A left lower lobectomy was performed on August 30, 1957. Specimens showed an arteriovenous aneurysm, about the size of a grape, projected into the superior surface of the lower lobe into the fissure, which was extremely thin-walled and could be seen to contain circulating blood (figure 7).

Postoperative convalescence was uneventful. The patient has been observed in the outpatient department and has remained well.

DISCUSSION

The diagnosis in the 3 cases presented here could be made from the family history, history of disease, radiologic findings, tomography, and selective angiocardiograms; in some cases, by cardiac catheterization; and in doubtful cases, by lung biopsy. As asymptomatic cases of arteriovenous fistula are usually found either upon mass radiography or on roentgenograms made for other reasons, these should be differentiated from the asymptomatic cases of specific and nonspecific inflammatory lesions such as tuberculosis, bronchiectasis, benign and malignant tumors, and so on.

In the symptomatic group, the arteriovenous fistula should be differentiated from congenital heart disease, polycythemia vera, chronic lung disease, and cyanosis which is caused by sulpho- and methemoglobinemia.

In the group of congenital heart diseases, patent ductus arteriosus or aortopulmonary septal defect, Fallot's tetralogy, and pulmonary atresia are the most common ones that should be taken into consideration. An arteriovenous fistula in the

left upper lobe with a continuous murmur may simulate patent ductus arteriosus. In patent ductus arteriosus or aortic pulmonary septal defect, there is usually a continuous machinery murmur, best heard in the first and second left inter-spaces, which may be associated with a thrill. Heart films will reveal enlargement of the left ventricle, dilation of the pulmonary artery, and pulmonary plethora, and x-ray screening will show a "hilar dance." Angiography will prevent mistakes in doubtful cases.

In Fallot's tetralogy, there is usually a systolic murmur with a thrill, the second heart sound is single because of absence of the pulmonary element, and venous and peripheral pulses are normal. A heart film will show right ventricular hypertrophy, absent pulmonary artery segment with minimal hilar markings, pulmonary ischemia, and right-sided thoracic aorta.

In pulmonary atresia, there is polycythemia, cyanosis, clubbing of the fingers, and a continuous murmur. However, angiograms will reveal bronchopulmonary anastomosis and show no main pulmonary artery. Tricuspid atresia is characterized by systolic murmur with a thrill and a single second heart sound caused by absence of the pulmonary element; an electrocardiogram will show P pulmonale and left ventricular preponderance. Roentgenograms of the heart will show enlargement of the left ventricle, dilatation of the right atrium, conspicuous aorta, hypoplastic pulmonary artery, and pulmonary ischemia.

Every case of symptomatic arteriovenous fistula will show a pulmonary lesion which immediately distinguishes it from congenital heart disease. The heart in arteriovenous fistula of the lung usually is not enlarged.

Physical examination in polycythemia vera will reveal an enlarged spleen and liver, and total white cell count may show many young forms. A transient thrombosis in the lungs may occur, causing densities in the chest film which may mimic multiple arteriovenous fistulae, but these densities disappear after a time.

Other diseases which should be taken into consideration in differential diagnosis are chronic lung disease, diffuse pulmonary fibrosis, and chronic emphysema, in which diseases there is inadequate oxygenation of the blood caused by lung lesions. In cyanosis caused by sulfo- or hemoglobinemia, there is no evidence of respira-

tory or cardiovascular disease, and laboratory investigations will help in differential diagnosis.

As the arteriovenous fistula of the lung may either rupture into the bronchus or into the pleural cavity, segmental resection, lobectomy, or pneumonectomy is advisable. The angiograms, however, should be made before operation to determine the number, size, shape, and location of arteriovenous fistulae.

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The Spinal Fluid

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OF ALL THE laboratory tests available to help supplement a neurologic diagnosis, the findings in the spinal fluid are the most helpful. Much too frequently, however, the spinal puncture is performed indiscriminately in patients in whom the procedure is contraindicated or is of no diagnostic help. Even more often, a spinal tap is performed and adequate studies are not carried out, necessitating a repetition of the procedure. It is for the foregoing reasons that an attempt will be made to point out the spheres in which the spinal fluid may be helpful and to emphasize the situations in which such a procedure should be avoided.

TECHNIC

The spinal fluid may be obtained by lumbar puncture or by cistern puncture. The lumbar puncture is the simplest method of gaining access to the subarachnoid space. The spinal cord terminates at the lower border of the first lumbar vertebra in the adult, and the arachnoid space continues to the second sacral vertebra. A needle can be introduced below the first lumbar vertebra without risk of injury to the cord. A spinal puncture is a technical procedure. *It should be carried out under sterile conditions and usually in hospitalized patients only.* The use of this procedure as an office technic should be discouraged.

The lumbar puncture can be performed with the patient either sitting or lying on one side. In either position, maximum flexion of the spine should be obtained. Landmarks, particularly the spinous processes, should be carefully determined. A line joining the highest points of the iliac crests passes between the third and fourth lumbar spines, and the puncture can be performed either at this point or at one vertebra

level higher. The skin is prepared with suitable antiseptics, and sterile drapes are placed around the puncture area. Sterile gloves should be worn by the physician, and only the hub of the needle should be touched. A sharp 20-gauge needle is best suited for this procedure in order to avoid unnecessary injury to the meninges.

Once the subarachnoid space is penetrated, the spinal fluid pressure must be measured with a water manometer, and, if the reading is elevated, the pressure should be observed for a few minutes and every effort made to obtain maximum relaxation of the patient. Queckenstedt's test (jugular compression in the neck) should not be routinely done. It is indicated only if spinal block is suspected. In cases of intracerebral pathology, it is contraindicated. If the fluid is blood tinged at first, it should be collected in several tubes after the pressure has been determined. If the fluid clears rapidly, the bleeding was probably produced by the puncture. Three or 4 tubes of spinal fluid should be collected for the usual tests. When the procedure has been concluded, the needle is withdrawn and the wound covered with a sterile dressing.

Cisternal puncture is a more complex procedure and should be done only by an experienced physician. It is done only if spinal puncture cannot be carried out at the normal sites. The patient's neck is shaved as high as the external occipital protuberance and the entire area carefully prepared with antiseptics and draped. A midline point is selected about 2 in. below the external occipital protuberance for insertion of the needle. The needle is advanced slowly, pointing slightly upward so that the occipital bone is encountered at a depth of 3 or 4 cm. The tip of the needle is then depressed and moved along the base of the occiput. Every few millimeters the stylet should be removed in order to make sure that the cistern has not been entered. The cistern is usually encountered at a

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depth of 4 to 5 cm. If the needle is inserted too rapidly and too deep, it will penetrate the medulla.

PROPER USE OF SPINAL PUNCTURE

Indications for spinal puncture

1. The chief use of the spinal puncture is to obtain fluid for cytologic, chemical, and other investigations that might aid in the diagnosis of the illness.

2. Spinal puncture is often used to introduce air into the subarachnoid spaces for diagnostic purposes. This procedure is referred to as an air encephalogram. It is used primarily in atrophic or degenerative lesions, old traumatic lesions, and in many cases of convulsive disorders. It is avoided when intracranial masses are suspected.

3. Spinal puncture is often done to introduce radiographic material into the spinal subarachnoid space for diagnostic purposes (myelography). Since the radiopaque material may be irritating to the subarachnoid tissues, it must always be removed when the studies are complete. This procedure is of value in the diagnosis of many spinal cord diseases, such as suspected tumors, herniated disk, obstructions due to spinal deformities, arachnoiditis, and so forth.

4. Spinal puncture has been used with too great frequency to introduce chemotherapeutic agents into the nervous system in cases of meningitis. Fortunately, this procedure has been greatly curtailed. At present, only streptomycin is still introduced intraspinally, and even this substance can be irritative to the subarachnoid tissues.

5. Spinal puncture is still used a great deal for spinal anesthesia in surgery. It must be kept in mind that these anesthetic agents can be irritative and may result in the delayed onset of radicular pain.

Contraindications to spinal puncture

1. Spinal tap should never be done in cases of high grade choked disk, especially in cases of suspected subtentorial tumor because of the danger of displacement of portions of the cerebellum into the foramen magnum and compression of the medulla, with consequent cessation of respiration and heart action. This medullary compression can be delayed and can appear many hours after the spinal tap. Before a spinal puncture is performed, a careful ophthalmoscopic examination must be carried out, and, if papilledema is present, the spinal puncture should be avoided.

2. Spinal puncture should be avoided in any patient suspected of having a subtentorial tumor even in the absence of papilledema.

3. Spinal puncture is best avoided in cases of respiratory paresis due to acutely developing central nervous system lesions.

4. Spinal tap should be performed with great caution in the presence of a possible spinal epidural abscess situated in the lumbar region. It is possible to introduce purulent material from the abscess into the subarachnoid space, thus producing a fulminating purulent meningitis.

5. Spinal puncture should be performed with great caution in patients with evidence of a large mass compressing the spinal cord. Sudden displacement of the tumor by the removal of spinal fluid may result in complete cord compression and a disastrous neurologic deficit.

6. In severely psychoneurotic patients, the spinal puncture is best avoided unless one strongly suspects concomitant disease, for which the procedure is diagnostically indicated.

ROUTINE SPINAL FLUID STUDIES

Pressure. The normal spinal fluid pressure is 100 to 150 mm. of water if the patient is recumbent or 300 to 360 mm. with the patient sitting. The pressure is increased in tumors, hydrocephalus, sinus thrombosis, and meningitis, while it often is reduced after repeated taps or in cases of spinal block.

Jugular compression in the neck produces a prompt rise and jugular release results in a somewhat slower fall of the pressure (Queckenstedt's sign). In a block at the foramen magnum or above the needle, there will be an incomplete rise and fall in the pressure on jugular compression and release. In such cases, pressure on the abdomen should produce a prompt rise in the pressure. A failure of the pressure to rise on abdominal pressure indicates a technical obstruction in the spinal puncture needle and not a spinal fluid block. Jugular compression should only be used in spinal cord lesions. It is contraindicated in intracranial lesions.

Appearance. Normally, spinal fluid is the color of water. Unclean tubes or an increase of the cells or protein alter the clarity of the fluid. A visibly turbid fluid contains more than 1,000 cells. In a bloody fluid, 500 to 1,000 cells result in a faint cloudiness; 1,000 to 3,000 cells make the fluid pink; while over 5,000 cells result in a red fluid.

Often, in a bloody spinal fluid, the question arises as to whether the blood is due to a traumatic tap or is actually the result of a subarach-

noid hemorrhage. The following procedures may prove helpful:

1. Collect the fluid in 3 successive tubes. A decreasing turbidity in each of the tubes suggests a traumatic tap.

2. Centrifuge the spinal fluid. If the supernatant fluid is clear, the tap was traumatic. In subarachnoid bleeding, the supernatant fluid is yellow.

3. The benzidine test may be helpful. To 1 cc. of spinal fluid add 1 cc. of benzidine in glacial acetic acid. Heat, cool, and add 1 cc. of hydrogen peroxide. A blue color indicates old bleeding due to subarachnoid hemorrhage and not a traumatic tap.

Cell count. Normally, the spinal fluid contains 3 to 5 mononuclear cells. If the tap is bloody, one should allow 1 white cell for every 700 red cells. Spinal fluid should be checked for tumor cells, yeasts, parasites, and so forth.

Protein. Normally, the spinal fluid protein is 15 to 40 mg. per cent. The ratio of albumin to globulin is 8:1. The protein is increased in venous stasis due to meningeal tumors; in vascular lesions, such as thrombosis; in inflammatory diseases of meninges with leukocytes; and in metabolic disturbances, such as peripheral neuritis and myxedema.

In some cases of almost complete block in the spinal subarachnoid space, there is a marked increase in the protein to over 500 mg. per cent. The spinal fluid is xanthochromic in color and coagulates on standing. This is called Froin's reaction.

The colloidal gold reaction in the spinal fluid is very helpful in neurologic diagnosis and is dependent upon the increased globulin in the fluid for its response. In carrying out this test, 10 tubes are employed, each containing the same amount of colloidal gold but decreasing concentrations of spinal fluid. The tubes are graded from 0 to 5 depending upon the amount of precipitation of the gold solution caused by the spinal fluid.

Sugar. Normal sugar values range from 50 to 80 mg. per cent. The sugar is increased in hyperglycemia and after intravenous glucose. Decreased spinal fluid sugar results in bacterial infections of the meninges.

Chlorides. The normal chloride value in the spinal fluid is 720 to 750 mg. per cent. In purulent meningitis, this value may be reduced to 650 mg. per cent. Some of the lowest values occur in tuberculous meningitis, where the level may drop to below 650 mg. per cent.

In cases of meningitis, observe careful bacteri-

ologic sterility. Before attaching the manometer, allow a few drops of fluid to flow directly into an appropriate culture medium. Collect 2 to 3 cc. of fluid in a sterile tube which can be used as the source of further bacteriologic culture techniques or for animal inoculation. In addition to the usual spinal fluid studies, at least the Gram's stain and stains for tuberculosis should be carried out. If the latter is suspected, a guinea pig should be inoculated with the fluid.

COMPLICATIONS OF SPINAL TAP

1. *Spinal puncture headache.* This condition occurs shortly after a spinal tap in a small number of cases. The patient has no discomfort while horizontal, but, when erect, a more or less severe headache develops which promptly disappears on lying down. The headache may last for days or even weeks and may be associated with some dizziness, occasionally nausea and vomiting, and sometimes stiff neck and signs of meningeal irritation.

This condition is apparently due to a leakage of spinal fluid through the arachnoid and dural membrane at the puncture sites. Attempts can be made to avoid this complication by making a clean-cut puncture with a sharp needle of small bore and by keeping the patient horizontal for twelve to twenty-four hours after the puncture in order to maintain the spinal fluid pressure low at the puncture site and thus allow the meningeal defect to heal. In the event that a headache develops, it should be treated by forcing fluids and by the use of 0.5 cc. of surgical Pituitrin intramuscularly.

2. *Medullary compression.* This complication occurs chiefly in the presence of posterior fossa tumors or in the presence of severe, increased intracranial pressure. It usually develops promptly during or shortly after the spinal puncture, although it may be delayed for hours. Clinically, the pulse becomes slow, blood pressure falls, and respirations are irregular. When medullary compression occurs following spinal puncture, immediate surgery is necessary to relieve the compression if the patient is to survive.

3. *Spinal cord compression.* In the presence of a movable tumor of the spinal cord, spinal tap can result in displacement of the tumor against the spinal cord with complete disruption of cord function. The sudden accentuation of symptoms readily reveals the correct diagnosis. Immediate surgery is necessary to save cord function.

4. *Meningitis.* This is an unusual complication and occurs as a result of a contaminated spinal puncture. If adequate precautions are instituted, this condition should not arise.

The spinal fluid can be almost diagnostic of certain diseases, while, in others, it may be of little or no help. The physician should be aware of the usefulness and limitations of this procedure and should use it accordingly.

Spinal fluid is diagnostic in:

1. *Acute purulent meningitis.* In untreated cases, the diagnosis is readily apparent by the extreme increase in polymorphonuclear leukocytes within the spinal fluid. The cell count may range from 500 to 20,000. Generally, the fluid is opalescent to purulent and shows a marked increase in protein—100 to 500 mg. per cent—and a reduction in the sugar to below 30 mg. per cent. In inadequately treated cases, the cell count may be only slightly increased, thus preventing an immediate diagnosis. In all cases, a search should be made for organisms and the fluid cultured for organisms.

2. *Tuberculous meningitis.* In the presence of a chronic lymphocytic meningitis, the spinal fluid findings may suggest a positive diagnosis. The fluid often is opalescent and shows a delicate fibrin web on standing. The cell count is increased to 50 to 200 cells, chiefly mononuclears, and the protein is increased to 100 to 500 mg. per cent. The most characteristic features are the markedly reduced sugar to below 30 mg. per cent and chlorides to below 650 mg. per cent. On repeated spinal taps, both the cell count and protein may show marked fluctuations in levels. Occasionally, polymorphonuclear leukocytes may be present. The fluid should be examined for organisms and inoculated into guinea pigs.

3. *General paresis.* The spinal fluid in an untreated case is often in itself diagnostic. The fluid is clear and contains 10 to 50 cells, chiefly mononuclears. The protein is increased to 50 to 150 mg. per cent. The most striking finding is the colloidal gold which shows a first zone curve. The spinal fluid serology is usually strongly positive.

4. *Spontaneous subarachnoid hemorrhage.* The diagnosis of this condition is apparent by the uniformly bloody fluid. The fluid shows many red blood cells, some of which are crenated. The spinal fluid pressure may be increased, and the protein may be moderately elevated. The red cells disappear in about one week, leaving a yellowish fluid.

5. *Spinal cord tumor with block.* In these cases,

the spinal pressure is often reduced, and Queckenstedt's sign is positive, showing no pressure rise on jugular compression. The spinal fluid is xanthochromic and contains a marked increase of protein, often as high as 1,000 to 5,000 mg. per cent. The cells are only slightly increased to 10 to 20 and are chiefly mononuclears.

Spinal fluid is suggestive in:

1. *Brain abscess.* Two spinal fluid findings should at least suggest the possibility of a brain abscess, namely, an elevated spinal fluid pressure and polymorphonuclear leukocytes in the spinal fluid. A similar picture can be produced by an extradural abscess or a sinus thrombosis, so that the spinal fluid changes must always be considered in conjunction with the clinical history and findings.

2. *Multiple sclerosis.* In about 40 per cent of clinically active cases, the spinal fluid will show a first zone colloidal gold curve. Otherwise, the fluid is normal. However, this finding alone in the presence of a suggestive clinical picture is strongly indicative of a demyelinating disease.

3. *Cerebral hemorrhage.* The spinal fluid is often helpful in substantiating the diagnosis. The fluid is xanthochromic or blood tinged, contains an increased number of red blood cells, and is often under increased pressure. It must be kept in mind that a sinus thrombosis, particularly in children, may produce identical spinal fluid changes, and the ultimate diagnosis must depend upon the total clinical picture.

4. *Guillain-Barré syndrome.* Generally, the spinal fluid is not too helpful, and the clinical manifestations must be relied upon for the diagnosis. In many cases, the spinal fluid protein becomes elevated to as high as 100 to 500 mg. per cent, and the cell count remains normal. However, one must keep in mind that in many neurologic conditions, such as diphtheria, peripheral neuritis, degenerative processes, and so forth, the spinal fluid protein becomes elevated and that such an isolated finding does not justify a clinical diagnosis.

Spinal fluid is of little help in:

1. *Viral infections.* Usually, the spinal fluid reveals mild, nonspecific lymphocytic meningitis.

2. *Brain tumor.* At best, the spinal fluid reveals only an increased pressure.

3. *Brain trauma.* Blood-tinged fluid may occasionally appear with brain trauma.

Electroencephalography in General Practice

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SINCE THE TIME of its discovery by Hans Berger in 1924, electroencephalography has steadily increased in importance as a diagnostic procedure for central nervous system disease. Not until after World War II, however, did standard, large-scale manufacturing of EEG machines in several countries cause this method to become available to every major hospital or clinic.

Perhaps because of its enormous contribution to the understanding of convulsive disorders and, to a somewhat lesser extent, to the diagnosis of brain tumors, other definite possibilities of electroencephalography as a diagnostic method are largely unknown except by specialists in the field. Only lately have internists and specialists of other branches, as well as general practitioners, begun to utilize the services of this technic in medical diagnosis. Several difficulties arise, however, when the nonneurologically trained physician tries to evaluate the results of an electroencephalogram, because the technic is so specialized that it is impossible for every physician to know its intricacies and the terminology used by the electroencephalographer. The electroencephalographer is frequently called by the referring physician, who usually seeks an "interpretation of the interpretation" of the electroencephalogram.

When the record is normal, no problem exists, but when it is abnormal, two extremes may be found among electroencephalographers. One extreme is exemplified by the very conservative and noncommittal report, "abnormal electroencephalogram," which does not, of course, give much information to the electrographically naïve

physician. Not even in simpler laboratory tests would this be adequate. If a doctor received a report about a glucose tolerance test which said only "Abnormal glucose tolerance test," he would not learn much. Merely to call an electroencephalogram abnormal is, thus, inadequate; it is not an interpretation but only a description of the record. It may be said by those who favor this method of reporting that the report contains, in addition to the general impression at the end, a more complete description of the record and that the type and degree of abnormality can be extracted from this detailed description. This argument is, however, not valid, because it would take at least some training in electroencephalography to be able to interpret the objective description of a tracing. This description provides a written picture of the record for future use of the electroencephalographer when he compares follow-up records on the same patient or when he analyzes a series of tracings for research purposes. The description should be, furthermore, complete and objective enough for another electroencephalographer to be able to get a concept about the record without having to rely on the first reader's impression. It is, however, the last impression, presented in a paragraph separate from the description of the tracing, which is going to be useful to the general physician.

The other extreme in reporting an abnormal record is the case in which the interpreter gives a very long list of possibilities involved in the given case; he may suggest the specific pathology of a possible tumor, for example, and may even give suggestions about treatment and further management of the patient. This is not only a waste of time for everybody but tends to discredit electroencephalography, as the diagnoses

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are very often incorrect because the electroencephalographer in this case ignores the limitations of the technic.

It is not only because of the electroencephalographer, however, that the usefulness of this method is diminished. The referring physician rarely gives sufficient information about the clinical picture in the request form, and the report, therefore, necessarily has to be limited to a description of the record, as electroclinical correlation is impossible in those cases.

Even in ideal cases, however, in which both the electroencephalographer and the referring physician fulfill their roles as such, there is wide margin for misinterpretation or lack of complete understanding of the report, because no diagnosis of a case can be made with a single laboratory procedure. Therefore, the physician will have to have enough understanding of the reports he receives to be able to correlate them with each other and with his clinical findings. In general, a personal conversation between the electroencephalographer and the referring physician gives complete satisfaction and answers all the questions that the physician may have in respect to the report. This is, obviously, not a practical system in most instances. It would be, therefore, very convenient if the general practitioner knew most of the indications and all the limitations of electroencephalography and if he knew also the meaning of some of the most frequent findings. This can be achieved without his having to go into the study of the technical or basic aspects of electroencephalography.

This article will discuss briefly some clinical aspects of electroencephalography which, we hope, will be useful for the general practitioner and for the specialist in nonneurologic fields.

A profitable approach to the problem may be to deal with it from the point of view of differential diagnosis of some commonly seen syndromes.

EPISODIC ALTERATIONS OF CONSCIOUSNESS

One of the most common conditions causing sudden loss or change in consciousness is epilepsy. When a good description is obtained, or by chance the physician witnesses a major motor seizure with tonic and clonic phases, loss of consciousness, and so forth, there is not much problem in deciding that it is a convulsive episode, and, most frequently, the patient is referred to a neurologist for further diagnostic studies and treatment.

There are, however, many instances in which the episodes are ill-defined and difficult to clas-

sify, even for the sophisticated specialist. Episodes of simple loss of consciousness without convulsions may be seen in syncopal attacks of different causes. The electroencephalogram may be extremely helpful in making a differential diagnosis between syncope and convulsive disorders. As a screening method, the general practitioner may order an electroencephalogram and, according to the result, decide later to refer the patient or to treat him.

A normal record does not exclude convulsive disorders, but chances are about 80 per cent against it in adults and 50 to 70 per cent in children, the percentage of accuracy increasing with the age of the child.

The presence of paroxysmal activity, especially of *spikes* or *spike-and-slow-wave complexes*, in the electroencephalogram is strongly suggestive of a convulsive disorder when the clinical picture is compatible with it. The presence of *random spikes*, either diffuse or focal, is also frequently associated with convulsions. If the report mentions seizure discharges, again in the presence of a clinical picture compatible with it, the physician almost certainly is dealing with a convulsive disorder.

If the record shows only diffuse abnormality or diffuse dysrhythmia nonspecific, and, if the diagnosis is not clear from clinical and other laboratory findings, activation of the electroencephalogram may prove very helpful.

Activation methods are defined in electroencephalography as those techniques used in addition to the routine record in order to bring out abnormalities not present in the resting tracing. The most common methods, used singly or in combination, are hyperventilation, sleep, photic stimulation, and Metrazol. Selection of the activation procedure and interpretation of the result have to be done cautiously, and it is probably desirable in most cases that the referring physician discuss these with the electroencephalographer.

A *slow wave focus*, in the presence of suspected convulsive disorders, may indicate a tumor. Space-occupying intracranial lesions are not the only causes of focal slow waves in the electroencephalogram, however.

A record that shows *diffuse abnormality of slow type* is compatible with several entities. If associated with episodic loss of consciousness, it could indicate convulsive disorders but also could be the expression of hypoglycemia. In both these conditions, the abnormality is frequently accentuated with hyperventilation.

If hypoglycemia is suspected, it is often help-

ful to perform a glucose or insulin tolerance test, taking short electroencephalographic tracings with each blood sample. It may be found that the record becomes markedly abnormal with levels of blood sugar not too far below normal. A clinical episode of the type of which the patient complains may be precipitated and may show correlation with increasing electrical abnormality.

Persistent electrical normality in the presence of episodic loss or alteration of consciousness even after activation procedures does not rule out seizures but is strongly against such a diagnosis.

In middle-aged or older people, cerebrovascular insufficiency may produce episodic alterations of consciousness, sometimes even associated with convulsions. During the stage in which the changes are episodic and no residual symptoms remain after episodes, the resting electroencephalogram may be normal. It also may be abnormal, however, showing focal slow waves. These can be brought out, when absent, by certain special procedures, but these methods should only be used by an experienced specialist. Compression of carotid arteries and other such techniques may be dangerous if not carefully controlled.

In children with simple febrile convulsions and with convulsoid states produced by hypocalcemia, the electroencephalogram is almost always normal, as distinguished from records in convulsive disorders.

STROKE SYNDROME

The stroke syndrome usually is easy to diagnose clinically. In some cases, however, a space-occupying lesion may have its first clinical manifestation in the form of a stroke. This is more frequent in children but also happens occasionally in adults. Electroencephalography often is helpful in the differential diagnosis in these cases. A single electroencephalogram, however, is not very useful. During the first few hours, or perhaps even the first day, after a vascular accident, the electroencephalogram may appear of very low voltage on the side of the lesion. In a short time, however, slow waves will appear and will become focal in a few days. If the electroencephalogram is taken at any time after this, the picture of focal slow waves will be the same as that found in tumors. Only if a second and, even better, a third record is taken will a change toward improvement in the case of cerebrovascular accident and either no change or progressive deterioration of the electrical

pattern, according to the rapidity of growth, in the case of tumor be noted. Thus it is important to repeat the record if the electroencephalogram is to be of real help in the differential diagnosis.

BEHAVIOR DISORDERS

Behavior disorders are especially frequent in children. Difficulties at school or at home are frequently seen and usually attributed to psychologic disturbance. In about 60 to 70 per cent of children with behavior disorders, an electroencephalogram will be abnormal. The types of abnormality change from case to case and probably represent, in many cases, a functional rather than an organic abnormality. In mentally retarded children or in children with obvious organic brain damage, the electrical pattern probably represents a manifestation of structural abnormality. In children with behavior problems but with normal intelligence and no physical signs or symptoms, it is not clear what exactly is the substrate of the electrographic abnormality.

If the abnormality consists of spikes, spike-and-wave complexes, or paroxysmal activity, thus suggesting some relation with convulsive disorders, anticonvulsants alone or combined with amphetamine frequently may be dramatically effective in controlling the abnormal behavior. The electroencephalogram is quite important for the diagnosis and treatment of these patients.

Some children have persistent episodic and unexplained abdominal pain that cannot be attributed to any reasonable local cause even after many diagnostic tests. If, in these cases, which sometimes present in addition behavior disorders, the electroencephalogram shows paroxysmal abnormality or spikes of any type, so-called abdominal epilepsy should be strongly suspected. In these cases, also, anticonvulsant treatment is in order.

Personality problems in adults, sometimes not clearly suggesting convulsive disorders, may be produced by the temporal lobe or limbic system type of epileptic disorder. In effect, some abnormal patterns of behavior which are not associated with amnesia for the abnormal episodes but frequently are caused by some sort of compulsion may be a manifestation of temporal lobe epilepsy. On occasion, the patient may be relatively aware of the surroundings but is not able to control his acts. This, of course, could be a purely psychotic phenomenon, but it also may be a form of convulsive disorder. The differ-

ential diagnosis is very important in these cases from the point of view of treatment and is, of course, in many instances, of medicolegal significance. In many of these cases, only the electroencephalogram can provide the clue to the diagnostic problem.

HEAD INJURY

It is not necessary to go into the details of the characteristics of an electroencephalogram after brain trauma. It is important, however, to understand the assistance that can be obtained from this diagnostic tool as well as its limitations.

In some cases, when loss of consciousness and other subsequent neurologic findings have resulted from direct injury to the head, there is no real problem in ascertaining that some brain damage, either temporary or permanent, exists. There are, however, cases in which, after some kind of injury that produces only secondary shaking of the head, such as the so-called whiplash phenomenon, marked but changing personality disorders appear. It is in these cases that electroencephalography is really helpful in the determination of cerebral dysfunction. This is, in many cases, the only objective finding. A normal electroencephalogram does not rule out brain damage, and an abnormal one does not necessarily mean that there is damage. It is important to be able to evaluate the electrographic findings in these cases.

Some mild diffuse abnormalities are present in a small percentage of individuals who are otherwise normal. As it is usually impossible to take an electroencephalogram before the injury, it is difficult in these borderline cases to determine how much of the abnormality may have been present previously.

In fairness to the patient, serial electroencephalograms are mandatory in these cases of questionable brain injury. After the injury, a series of processes starts, and one electroencephalogram at a given time will only give an idea of one instant in that continuously changing chain of events. If the pattern becomes either more abnormal or more normal as the series of electroencephalograms progresses, the physician may legitimately assume that a relatively recent cause produced this changing series of tracings. Changes are not prominent from one record to the next unless some active process is present. In some cases, the initial mild diffuse abnormality may change in three or four months to a completely normal and clearly different pattern. It is logical to assume that the mild abnormality was caused by a recent event, and, if this event were trauma, by the injury.

Even a clearer case is that in which the first postinjury electroencephalogram is either normal or mildly abnormal and the subsequent records in a follow-up series become increasingly abnormal. Other circumstances being equal before and after the injury, it is difficult to escape the conclusion that the trauma was the cause of the electrical abnormality.

In most cases, the electrical changes found soon after head injury are diffuse and of the slow wave type. If the injury is severe enough, this will change to focal abnormality that may consist either of slow waves or of spikes. It is, however, not very unusual to see spikes a few weeks and even a few days after trauma.

It is not easy to prognosticate the future clinical condition of a patient subject to head injury on the basis of an electroencephalogram or even of a series of them. There is not enough knowledge of the subject; therefore, although the future pattern in a given patient may sometimes be predicted, a clinical correlation with this electrical pattern cannot be foreseen.

NON-NEUROLOGIC CONDITIONS

In metabolic disease of the type caused by liver dysfunction, sudden changes in the clinical status of the patient may be found without much warning. The liver function tests are usually good indicators, but there is a limit to the frequency with which these tests may be requested.

It has been reported frequently that, in cases where the patient's mental status is clear, in the presence of liver disease with no evidence of central nervous system alteration, the electroencephalogram becomes definitely abnormal, sometimes several days before the onset of hepatic coma. Specific electrical abnormalities have been reported in association with this pre-coma state, but, even in their absence, a definitely abnormal electroencephalogram in a patient with liver disease is a reliable warning of impending hepatic coma.

In the dramatic situation of cardiac arrest, either during anesthesia or in other circumstances, not many people think of obtaining an electroencephalogram of the patient. This is, of course, understandable, as there are emergency measures that have to be taken in order to try to save a life. After the acute emergency is over, however, it is important to be able to make a prognosis, at the same time as active treatment is continued.

If an electroencephalogram is made and shows, after eight or twelve hours, no electrical activity, that is, a flat record or an isopotential record, the prognosis for normal recovery is

poor. If, on the other hand, diffuse slow waves are present and gradually become more normal, the prognosis is good and complete recovery and normal function can be expected.

SUMMARY

The electroencephalogram can be of great usefulness in the diagnosis and prognosis of conditions frequently seen in general medical practice. However, the full use of this diagnostic tool is generally not made available to the general practitioner and nonneurologic specialist, mainly due to deficient communication between electroencephalographer and referring physician.

It is necessary to understand the electroencephalogram as the expression of dynamic proc-

esses and not to take a single record as being representative of the pathologic condition. If this is understood, if the referring physician has some knowledge of what to expect in the different situations, and if both the electroencephalographer and the referring doctor fulfill their respective roles when an electroencephalographic study is planned and performed, a definite and outstanding service will be given to the patient.

Some of the main conditions in which the electroencephalogram will be of help to the medical practitioner have been analyzed. A gross outline of the types of electrical abnormalities found in those conditions has been presented so that interpretation without extensive knowledge of electroencephalography is possible.

PERSONS who wear binaural eyeglass hearing aids are more satisfied than persons using monaural devices. Acceptance by the patient may be the most important criterion influencing successful use of a hearing aid.

The advantages attributed most often by patients to binaural aids are the ability to hear twice as well; better understandability in general; personality improvement, such as less nervousness and strain, more active social life, and greater interest in television and radio; ability to hear better in a group; more accurate sound localization; and equalization of sound. Less frequent benefits reported include more natural sound, elimination of clothing noise, better hearing from a distance, more sensitive modulation of volume, and the opportunity, if one side is defective, to use the other aid as a spare. These subjective advantages are not measurable, but, possibly, binaural hearing promotes an intra-aural effect reflected in better sound balance and greater acuity of perception, even though the intelligibility score is identical with the monaural score.

Criticisms by binaural aid users mainly concern the price of the aid, cost and defects of the batteries, improper fit of the earmolds, and extraneous noises, that is, electronic sounds generated by the aids, coupled with acoustic feedback and environmental sounds traceable to poorly fitted earmolds. For the binaural user, defective and short-lived batteries are a dual source of irritation. When the earmolds or tubing permits acoustic feedback, professional adjustment is imperative.

A total of 50 successful binaural eyeglass hearing aid users were polled by questionnaire, and the answers were compared to the results of 2 previous investigations of monaural hearing aid users. Of the binaural users, 42 per cent had no criticisms of the aid, compared to 30 per cent of the monaural users.

F. KODMAN, JR.: Successful binaural hearing aid users, *Arch. Otolaryng.* 74:302-304, 1961.

The Indeterminate Lung Lesion

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MANY PULMONARY DISEASES present a characteristic x-ray picture from which a tentative diagnosis may be made with a fair degree of accuracy. Anyone, be he a general practitioner, internist, or surgeon, who is dealing frequently with lung diseases will be confronted sooner or later with a number of atypical x-ray lesions which we characterize as indeterminate lung lesions. These present no characteristic appearance and may offer a rather difficult diagnostic problem. They fall into 3 general categories: the diffuse lesions, which can be bilateral; the localized infiltrates, usually unilateral; and the isolated nodular lesions, often mis-called coin lesions.

Making an accurate diagnosis in some instances is relatively simple, while in others, it may be extremely complex, with the correct diagnosis being reached only after a painstaking study utilizing all possible diagnostic means. A complete comprehensive history covering many phases of the patient's existence and a thorough physical examination, including all systems, followed by numerous tests and laboratory procedures may be required before the proper answer is reached.

The sequence of these various tests will, of course, vary with the type of lesion presented and the clues turned up by the various investigations. Much latitude and discretion must be exercised at all times and a set routine avoided if unnecessary delay and expense is to be obviated. Detective work of a high degree may be needed at times to solve a very puzzling problem.

HISTORY

The importance of a complete, thorough, and detailed history of many facets of the patient's existence cannot be overemphasized. The family history, especially concerning asthma, hay fever and other allergic traits, emphysema, bronchitis, hypertension, vascular disorders, cutaneous telangiectasis, nose bleeds, hemorrhagic tendencies, and so forth, must be delved into. The occurrence of tuberculosis among members of the family, friends, co-workers, or associates must always be

sought. The patient's place of residence, now and in the past, may hold the clue to a number of diseases; travel to various areas and military service must be ascertained if all possible localities of exposure are to be considered. Residence in or visits to territories where specific diseases are endemic may give valuable clues. Some diseases, such as coccidioidomycosis, occur in certain areas of California, Arizona, New Mexico, Texas, and Mexico, and others, such as histoplasmosis, in the Ohio and the lower Missouri valleys and in certain areas of Minnesota. Even visits of short duration may be important, a vacation, a hunting trip, or even a car trip through certain areas being sufficient for exposure.

Personal habits may also be important. Smoking, particularly excessive and prolonged cigaret smoking, certainly is a factor in bronchitis, bronchiolectasis, and emphysema, while its association with bronchogenic carcinoma, squamous-cell type, cannot be easily discarded. The use of chewing tobacco and snuff, associated with poor dental hygiene, may be pertinent to the difficulty. The presence of *Pseudomonas* and certain fungi in both of these products may be relevant to the problem. Drinking habits, also, or a drinking bout to stupefaction, with vomiting, may be the cause of the patient's trouble.

OCCUPATION AND OTHER ENVIRONMENTAL FACTORS

Occupation is an especially important factor in some of the diffuse pulmonary lesions. Foundry workers, hard rock miners, coremakers, sand blasters, quarry men, granite workers, and others are exposed to silica dust. Machinists, casters, grinders, and plating and polishing workers may be exposed to a variety of metallic substances which may cause lung changes. Welders are exposed not only to the fumes of their welding but to a number of metallic materials. Workers with beryllium, as in the manufacture or breaking of fluorescent lamps or making of neon signs or radio tubes, may acquire berylliosis. Even locations within short distances of factories where such things are handled may be subject to contamination. Workers handling insulating material may be exposed to asbestos or rock wool dust

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which can produce lesions. Grain elevator workers are subjected to a variety of dusts, not only from soil but from grain contaminated with smuts and molds, which may produce complications. Fungus infections have been reported from working with some woods and wood products.

Laboratory workers may be exposed to a variety of irritants or infectious materials. Workers with a variety of sprays may inhale harmful substances. Farmers may be exposed to noxious gases from fermenting silage and to molds from moldy hay, grain, or silage, both of which can produce lung lesions. Workers exposed to the fumes from refrigeration equipment may sustain toxic effects from chlorine, sulfur dioxide, and other noxious chemicals. Workers employed in dusty places, particularly attics, abandoned buildings, belfries, chicken coops, and even bat-infested caves and other places where there may be droppings from chickens, turkeys, pigeons, and bats, may acquire histoplasmosis from such sources.

Animals. Pets or animals of various types must also be considered; parrots, parakeets, and budgies may harbor the organism of psittacosis. Cows, pigs, and goats may be affected with brucellosis. Turkeys and pigeons may be affected by histoplasmosis and a number of other fungus diseases. Ticks from infected animals may transmit spotted fever, tularemia, and other diseases. Rabbits or game birds may transmit tularemia to the incautious hunter. Some soils, especially from around chicken coops or under trees used by roosting birds, as well as some fertilizers, may carry the spores of histoplasmosis.

Diseases. A personal history of allergy, eczema, hay fever, asthmas, or drug sensitivity may be basic in the recognition of some puzzling lung lesions. A special history of previous surgery must not be overlooked, for a tumor removed from elsewhere in the body, even years earlier, may be relevant to the situation. Previous treatments for moles or other skin defects, particularly those treated without biopsy of the lesion; fracture; surgery; delivery; or prolonged immobilization in bed, with or without the clinical picture of phlebitis or thrombosis, must be evaluated. The tendency toward thrombosis in certain patients with malignant tumors must also be recognized. A long period of sitting or kneeling in a canoe, car, boat, or bus or long periods of dangling with the feet over the edge of the bed may likewise predispose to thrombosis and subsequent embolization.

Other conditions. The possibilities of aspira-

tion of material into the lung must also be given due thought. Foreign bodies of a metallic, shadow-casting variety are easily recognized, but the nonopaque types are frequently overlooked. There may be a definite history of an episode suggestive of aspiration, but all too often, materials are aspirated when the patient is under anesthesia or is unconscious or semiconscious from sedatives, alcohol, diabetic coma, head injury, or cerebrovascular accident and thus has no memory of the occurrence. The material need not be recognizable as a foreign body; food, stomach contents, material from a tonsillar crypt, or pus or tartar from around infected teeth can cause equal harm. Oily nose drops or sprays, greasy material applied or sniffed into the upper air passages, or mineral oil or its derivatives taken to alleviate constipation may be aspirated into the lung without the patient's knowledge. Neurogenic disturbance of the swallowing mechanism or disturbed sensation of the pharynx and larynx, as in poliomyelitis or other neurogenic lesions, may permit aspiration of material if the patient attempts to swallow. Material accumulated in the esophagus in achalasia, in a pharyngeal diverticulum, or proximal to an obstructing carcinoma of the esophagus may spill over into the trachea and produce lung trouble. A perforating carcinoma from the esophagus to trachea or bronchus may permit aspiration into the lung and produce a bizarre type of pulmonary disease.

Intensive study. A rough outline for the study of these puzzling situations should include: (1) history, (2) physical examination, (3) roentgenographic examination, (4) laboratory studies, (5) bronchoscopy and bronchography, (6) surgery, and (7) observation. Some lesions cannot be identified on single examination but may have to be followed for a considerable period before a definite diagnosis can be reached. In such a case, repeated observation, not only of previous x-ray films but of films made over a period of time in the future, may be of great value. To sum up, a thorough and complete study of the patient by all means at hand may be necessary and certainly is advisable in the study of these patients.

DIFFUSE LESIONS

There are literally dozens of conditions which may present as extensive or diffuse pulmonary infiltrations unilaterally or bilaterally. They vary so much in appearance in different instances that the films of one condition might well be exchanged for those of another without anyone's being the wiser. Just a few of the more common

causes of such diffuse lesions are here listed in a rough but not absolute order of frequency, as this will vary with the physician's type of practice.

Diffuse Lesions

Pulmonary tuberculosis	Aspiration pneumonitis
Miliary tuberculosis	Oil pneumonitis
Sarcoidosis	Histoplasmosis
Silicosis	Löffler's syndrome
Silicotuberculosis	Brucellosis
Primary atypical pneumonia	Lupus erythematosus
Bronchiolar carcinoma (alveolar cell)	Scleroderma
Farmer's lung syndrome	Asbestosis
Silo filler's disease	Berylliosis
Bronchiectasis	Hemosiderosis
Emphysema	Psittacosis
Bronchogenic carcinoma	Cryptococcosis
	Metastatic carcinoma
	Alveolar proteinosis

When confronted with a picture of a diffuse lesion, the following list of studies may be of help in unraveling the diagnostic problem: (1) A good history may and frequently does give a clue which makes an accurate diagnosis possible. (2) Physical examination may provide information in both a positive and a negative way to give clues to indicate special examinations. (3) Sputum examination, if such is available, should include special studies for tubercle bacilli, cancer cells, fungi, and cultures for secondary organisms and their sensitivities, at times including anaerobic as well as aerobic cultures. (4) Skin tests for tuberculosis, histoplasmosis, coccidioidomycosis, and, at times, blastomycosis or actinomycosis should be made and repeated, if necessary. Complement fixation and agglutination tests will occasionally be of value. (5) Special x-ray studies may add much to our knowledge, particularly the lateral projection in conjunction with the ordinary posterior-anterior films. Lordotic films will reveal the apical regions. Planigrams, both anterior-posterior and lateral, will outline tumor, bring out calcareous deposits, and outline the bronchi or bronchial obstruction. Bronchograms, properly made, may add much valuable information. (6) Blood studies, including the leukocyte count, differential blood count, sedimentation rate, agglutination tests, and complement fixation tests, are of use in certain situations. (7) Bronchoscopy is useful not only for demonstrating tumor, foreign body, obstruction, and deviations of position but also for obtaining secretions, bronchial washings, and biopsy material for study and for clearing the bronchi preparatory to bronchograms, which can then outline the more distal portions of the bronchial tree. (8) Tissue biopsy frequently is necessary in order to establish a definite diagnosis.

Direct bronchial biopsy, aspiration, or bronchial wash is perhaps most frequently employed, especially in the diagnosis of tumor. Biopsy of the bronchial mucosa at the carina may give as high as 50 per cent positive results in sarcoidosis, even though the tissue appears to be grossly normal. Biopsy of lymph nodes, especially from the prescalene area and from the axillary region, is perhaps most valuable. Occasionally, nodes at a more distant site may give the answer. Bone marrow biopsy may help make the diagnosis of miliary tuberculosis, leukemia, sarcoidosis, and, occasionally, rarer conditions.

Lung biopsy through a buttonhole incision may give characteristic material to establish a diagnosis but gives no assurance of obtaining the most characteristic material for study. Thoracotomy with lung biopsy will, of course, provide the final clue to diagnosis in many of these conditions, but it must be remembered that, in the patient with extensive bilateral pulmonary disease, such a procedure must not be undertaken too lightly, because, in the patient with markedly diminished vital capacity, it carries with it a very appreciable mortality.

Before doing some of the more extensive and at times somewhat heroic diagnostic procedures, serious thought should be given to the fact that, of the many conditions which may present these extensive diffuse pulmonary infiltrations, we have in our armamentarium specific agents for the control of only a few. From the patient's standpoint, therefore, the diagnosis is largely of academic interest, and the extensive work-up that might be advisable and justifiable in a public teaching institution can scarcely be justified financially or morally for the average patient presenting these conditions. He is more interested in obtaining relief than in completing a chart record.

A few of the pertinent diagnostic points about the various conditions would be of interest.

Pulmonary tuberculosis. Tuberculosis has not been eliminated from our population. It still exists, and many advanced lesions of both new and recurrent types are still being seen. It occurs in the aged as well as in the young. It should be the number one suspect in all such lesions. Check the history, check the Mantoux test, examine all sputum by smear and culture, view all x-ray films, and do not be misled by one or two negative sputum tests. Many diffuse lesions should be considered tuberculous until proved otherwise.

Miliary tuberculosis. The fine, bilateral, miliary type of lesion should first be suspected of

being tuberculous. Fever and dyspnea occur commonly. The presence of other tuberculous lesions, meningeal symptoms, and progression of the lesions speak in favor of miliary tuberculosis. A Mantoux test usually will be positive but may not be if the patient is overwhelmed. A study of the eye grounds may reveal tubercles. Bone marrow biopsy may reveal a typical granuloma or acid-fast organisms. A study of sputum and urine by smear and culture may be of help. The appearance of the lesion after pulmonary hemorrhage should be suggestive of bronchogenic spread. With modern intensive drug therapy, the prognosis is not hopeless.

Sarcoidosis. Diffuse pulmonary infiltrations associated with enlarged hilar nodes and in particular the right paratracheal node should suggest sarcoidosis. The tuberculin test, repeated, should be negative. The sputum, of course, will be negative. There may be a febrile onset with few or no symptoms, and dyspnea may or may not be present. If the condition is chronic, it may persist over many months but may eventually clear almost completely. The scalene lymph node biopsy will be positive in at least 75 per cent of cases. Biopsy of the mucosa at the carina will give approximately 50 per cent positive results. The Nickerson-Kveim test in the hands of those who have used it extensively may be of some value but has little value for the occasional user. The albumin-globulin ratio may be disturbed. The electrophoretic pattern may provide some information.

Silicosis. The x-ray picture here may be very variable, from multiple, small miliary lesions early in the course of the disease to extensive infiltrates on one or both sides, with or without the typical angel-wing infiltrates extending out from the hilar regions, in the later stages. Dense nodular infiltrates may appear later, with or without cavitation. When the disease becomes nodular or cavitation is seen, the possibility of a superimposed tuberculosis must be considered.

Mantoux tests, sputum examinations, and gastric cultures for tuberculosis should be made. The work history is all-important in making the clinical diagnosis. Progression of the process is usually slow but may be rapid, depending upon the intensity of exposure. The disease may progress even after all contact has been broken. Fever and dyspnea are usually not present until late, when secondary infection, emphysema, and bronchiectasis cloud the picture. Disability must be judged on impaired function rather than on the appearance of the roentgenogram.

Bronchiolar or alveolar cell carcinoma. This may start as a local focus, frequently in an upper lobe, later becoming an extensive bilateral nodular process. The progression may be rapid or may be extremely slow, extending over a period of a few years. A profuse mucoid secretion sometimes described as characteristic of this lesion occurs only as a very late symptom; dyspnea appears as respiratory capacity is reduced. The study of lung secretions, lung biopsy, or bronchial biopsy may establish the diagnosis.

Farmer's lung or moldy hay disease. This disease of farmers who have been in contact with moldy hay or silage frequently has its onset with fever, chills, dry cough, general malaise, dyspnea, and weight loss, usually diagnosed as "flu." Later, the sputum may be mucopurulent, occasionally blood-streaked, and may show *Candida albicans* on culture, though no one is sure that this is the cause of the condition. The history is very important in making the diagnosis. The process will usually clear when the individual is removed from the proximate cause and will recur with additional exposure to the same conditions. The use of a dust muzzle or removal from the environment is the answer.

Silo filler's disease. This condition of the lung is caused by inhalation of nitrogen dioxide produced by the fermenting of silage in the early days after the silo is filled. It occurs in individuals who have gone into the silo or the silo pit within about ten days after it has been filled. This brownish vapor is heavier than air and sinks down to dependent locations, where it may kill pigs, chickens, or calves who wander into the contaminated area. The gas produces an acute type of pneumonitis with pulmonary edema, which may appear at once or, if inhaled in smaller amounts repeatedly, may be delayed as long as two or three weeks. If the exposure is intense, it may be rapidly fatal, producing massive pulmonary edema, obliterative capillary bronchitis, and extreme dyspnea. The history gives the clues to the diagnosis.

Bronchiectasis. Extensive bilateral pulmonary infiltration may be produced by bronchiectasis or chronic cystic disease in the lung without the characteristic picture or typical sputum of ordinary localized bronchiectasis. The association with chronic emphysema may produce a very confusing clinical and roentgenographic picture which can only be recognized by functional lung studies and bronchograms.

Bronchogenic carcinoma. Primary bronchogenic carcinoma usually presents a localized unilateral infiltrate or obstructive lesion. Some

patients who are seen late in the course of the disease present an extensive bilateral infiltration from lymphatic obstruction or extension or diffused bilateral nodular infiltration. Frequently, there will be a localized infiltrate or atelectatic area representing the primary lesion, but this is not always so. The diagnosis frequently may be made by study of sputum for malignant cells, by bronchoscopy and biopsy, and, possibly, by scalene lymph node biopsy.

Aspiration pneumonitis. Aspiration pneumonitis may occur for a variety of reasons and conditions. Pneumonitis may follow the use of mineral oil or oily nose drops over a long period. Aspiration may occur after a period of unconsciousness for any reason or as a result of difficulty in swallowing from neurogenic disease or esophageal spillage; or a pharyngeal diverticulum, achalasia of the esophagus, or an esophageal stricture; or of carcinoma or foreign body obstruction. The process may be localized or diffuse and with or without pulmonary abscess.

Miscellaneous. There are a wide variety of diffuse pulmonary lesions which may follow inhalation of many industrial dusts and products, sprays and paints, industrial gases, refrigeration gases, and various fungus and viral diseases too numerous to be covered in this discussion.

LOCAL INFILTRATIONS

Local infiltrations present more numerous and perhaps more important diagnostic problems than diffuse lesions. Certainly, they require and perhaps deserve more careful study than the other groups because they are more confusing and because much more can be done for and about them. The first thing to consider, when confronted by an isolated pulmonary infiltrate, is the possibility of pneumonia. A careful history, physical examination, and response to definitive treatment will usually soon answer this question. Blood and sputum studies aid greatly. Ordinary pneumonia responds quickly, particularly if sensitivity studies have been made and the appropriate antibiotics administered. If response is not obtained within a couple of weeks or if resolution is not complete, additional studies should be made and other possibilities considered.

There are two diagnostic terms which I do not like—viral pneumonia and unresolved pneumonia, both of which may occur. The reason I do not like them lies in the fact that, as soon as one makes such a diagnosis, he immediately treats the patient for this condition and expects poor response and slow clearing of the present-

ing lesion, thereby losing valuable time. This may not only jeopardize the patient but, if the process be tuberculous, perhaps cause contamination of other individuals while waiting for the lesion to clear.

Unresolving or slowly resolving lesions may be any one of the conditions here listed and perhaps many more.

Local Infiltrations

Pneumonia	Foreign body syndrome
Tuberculosis	Hodgkin's disease
Viral pneumonia	Metastatic carcinoma
Middle lobe syndrome	Löffler's pneumonia
Bronchogenic carcinoma	Bronchiolar carcinoma
Atelectasis	Radiation fibrosis
Bronchiectasis	Primary tuberculosis
Pulmonary abscess	Histoplasmosis
Friedländer's pneumonia	Blastomycosis
Infarction	Actinomycosis
Oil pneumonitis	

When confronted with such a situation, the physician should realize that he has a diagnostic problem on his hands and get busy making the proper diagnosis.

Perhaps the second most frequent cause of a local infiltrate is tuberculosis, usually in the apical and posterior segments of the upper lobes of the lung but possibly involving any segment. The presence of bloody sputum, free bleeding, or cavitation may aid in recognition of the condition. Repeated sputum studies by smear and culture, gastric cultures, and Mantoux tests should be made without delay. If the condition is suspected, the patient most certainly should be isolated to protect other patients and the nursing personnel involved in the patient's care.

Primary atypical pneumonia or viral pneumonitis or influenza must next be considered. Failure of a process to respond to chemotherapy must certainly cause a physician to raise his eyebrows on a diagnosis of ordinary pneumonia. Segmental obstruction, such as occurs in the middle lobe but which may also occur in various segments of other lobes, must be considered and recognized.

High on the list of conditions to be considered with a pneumonic process that does not clear promptly is bronchogenic carcinoma. The physician must always carry a very high index of suspicion for this lesion in any slowly resolving or nonresolving infiltrative process in the lung in patients beyond the age of 30. It may occur in even younger individuals but does so much less frequently. Primary bronchogenic carcinoma can mimic any other disease of the lung. The symptoms from it at onset are frequently those of an ordinary pneumonitis, produced by infection in

the obstructed area. Failure to respond, however, should alert the physician to its possible presence.

This whole group of conditions calls for a most thorough work-up along the lines previously described. Detailed studies should be determined by the clues which are brought out and by findings previously elicited. There must be no delay initiating or carrying through the studies, for time is extremely important in many of these conditions. Primary bronchogenic carcinoma has never been cured by penicillin or other antibiotics, nor has wishful thinking ever eliminated it. It is a metastasizing lesion. A month's delay may mean the difference between resectability and possible curability and a hopeless prognosis—hence we must not wait two months for a report of tuberculosis cultures.

If a physician does not possess or have available the experience or the special technics necessary for the further study of these conditions, he should not hesitate to refer the patient at once for the special studies indicated. Better to subject a dozen patients to intensive studies to rule out carcinoma than to miss one at an early stage. There is no conservative treatment for this condition.

There are no happier or more grateful patients anywhere than those under the cloud of a possible bronchogenic carcinoma who can be proved not to harbor this condition and in whom another and more favorable condition can be proved. In spite of all our knowledge about this condition, far too many patients are seen and diagnosed in the late stages of bronchogenic carcinoma.

Studies here should be along the lines previously outlined, with special emphasis placed on cell and sputum studies, bronchial aspirate and washings, bronchoscopic examination and biopsy, bronchograms, and scalene lymph node biopsy. If these fail to establish the diagnosis, an exploratory thoracotomy with excision of the offending lesion and immediate pathologic examination should be performed.

Local infiltrative lesions, unlike the diffuse ones previously described, present many possibilities for alleviation or elimination of the condition by intensive chemotherapy, surgery, or radiation therapy. A brief discussion of a few of these conditions may be of interest.

Middle lobe syndrome. The middle lobe syndrome frequently, though not always, results from obstruction of the middle lobe bronchus by extrinsic pressure from enlarged lymph nodes surrounding it, producing atelectasis and, even-

tually, secondary bronchiectasis. It may or may not be symptom-producing at the moment but often gives rise to recurrent bouts of pneumonitis. Cough, expectoration, hemorrhage, fever, wheezing, and pleuritis may occur. The syndrome may be caused by an obstructing tumor within the middle lobe bronchus, but this is not common. A similar process may occur in any segment of any lobe, but the middle lobe is most prone to such involvement.

Bronchiectasis. Localized bronchiectasis may or may not be symptom-producing. Frequently, it cannot be recognized without bronchoscopic and bronchographic visualization and may respond temporarily to antibiotic therapy. If there is recurrent pneumonitis, profuse or foul sputum, or severe or recurrent pulmonary hemorrhage, local excisional therapy is curative.

Pulmonary abscess. Pulmonary abscess usually results from aspiration of material with or without retained foreign body. Rarely, it occurs from a septic embolus. Usually, it does not respond to the ordinary doses of antibiotics, but with sensitive organisms it may respond to king-size doses and clear completely. The history will often give a clue to its origin. The character of the sputum and presence of cavitation as seen on ordinary films or on planigrams may help to make the diagnosis. If the condition does not respond promptly to intensive chemotherapy, excisional surgery is indicated.

Friedländer's pneumonia. Friedländer's pneumonitis frequently has a history of preceding aspiration. Multiple cavitations may be seen. The diagnosis is made on culture, with identification of the offending organism. The disease may respond to intensive chemotherapy, but some local lesions which have become chronic may eventually have to be resected.

Pulmonary infarction. Pulmonary infarcts occur far more frequently than they are recognized. Less than half of them present the characteristic picture of a preceding phlebitis or phlebothrombosis followed by sudden onset of chest pain, expectoration of blood, dyspnea, and the appearance of pulmonary infiltration. Infarction may occur in any segment of the lung, though frequently in the lower half. Infarcts may be multiple or recurrent and will be recognized as such only if the clinician is eternally alert to the possibility of such a condition.

Oil pneumonitis. Oil pneumonitis is frequently a chronic process. Its etiology is frequently obscure unless specific questioning is made of such a possibility. It occurs in both children and

adults and is often confused with other lesions, including bronchogenic carcinoma. A detailed history is most important.

Löffler's syndrome. The shifting, patchy, recurrent pneumonitis of Löffler's syndrome is an allergic phenomenon perhaps associated with some eosinophilia and is recognized by the shifting character of the infiltration.

NODULAR DISEASE

Isolated pulmonary nodules, often miscalled coin lesions, are usually discovered on routine examination and are almost always asymptomatic. The more common, though certainly not all, possible causes are as follows:

Tuberculosis	Brucellosis
Histoplasmosis	Arteriovenous fistula
Bronchogenic carcinoma	Metastatic carcinoma
Hamartoma	Breast
Fibroma	Kidney
Adenoma	Ovary
Mesothelioma	Colon
Primary tuberculosis	Chorion
Coccidioidomycosis	Small intestine
Cyst	Sarcoma

Formerly, many of these lesions were called tuberculomas, even by the pathologist, but we now recognize that many of the inflammatory lesions are not the result of tuberculosis. The term granuloma is more accurate, and tuberculoma should not be used unless the lesion's tuberculous etiology can be proved. When confronted with such a lesion, one should routinely do a tuberculin test, repeating it if necessary. Skin tests for histoplasmosis, coccidioidomycosis, and blastomycosis should also be made. First of all, be certain that the rounded shadow on the x-ray film lies within the lung and is not extrinsic to it. Moles and tumors on the skin, a nipple shadow, a breast tumor, and buttons or other articles on the clothing may be mistaken for a pulmonary nodule.

The position in the lung should be determined by posterior-anterior and lateral chest films. The density of the shadow should be evaluated in comparison to its size. Overexposed films or planigrams should be made to determine the presence of calcium, satellite nodules, concentric ring structure, or cavitation within the confines of the nodules. If there are any previous x-ray films available, they should be reviewed in order to determine how long the nodule has been present, whether or not it has grown, or what lesions may have preceded the appearance of the present nodule. The age and the sex of the patient must also be taken into considera-

tion, for malignant lesions are rare under the age of 40 and are more likely to be found in men than in women.

By and large, as we see these nodular lesions, 40 per cent are granulomatous; 40 per cent are malignant, either primary or secondary; and 20 per cent are benign tumors, cysts, and rarer lesions. In men over the age of 45, 60 per cent of such nodules will be malignant. Marked density in a small lesion—under 1 cm. in diameter—or the presence of calcium greatly reduces the percentage chance of malignant disease. The presence of calcium, however, does not completely eliminate the possibility of a malignancy, for a few primary and some secondary malignant lesions have been reported with calcium in or adjacent to the tumor mass.

The finding of a positive tuberculin, histoplasmin, or coccidioidin test does not prove that the nodule in question is caused by that etiologic agent. The presence or absence of growth of the lesion on serial films affords no certain proof concerning the benign or malignant nature of the nodule in question, for we have seen malignant nodules displaying no growth over periods of three or four years and, on the other hand, have observed definite evidence of growth in tuberculous and histoplasmosis nodules, adenomas, hamartomas, fibromas, mesotheliomas, and cystic lesions—all benign. The possibility of the nodule being metastatic from a primary tumor elsewhere is always a speck in the picture.

A good history, physical examination, and perhaps some screening should be undertaken. It is unnecessary, however, and usually inadvisable to do a routine x-ray screen of all other systems and organs unless there is something definite to point to possible primary tumor elsewhere. No one, no matter what his experience, can with certainty predict the exact nature of more than the occasional nodule. The surgeon or the pathologist with the lesion in his hand cannot usually make an accurate diagnosis without some further study. There is little to be learned from bronchoscopy or cell studies in most of these peripheral lesions, and only rarely does the information gained by special cultures justify the delay necessitated in waiting for them. Unless there is some contraindicating factor or unless we are dealing with the very young, in whom the incidence of malignancy is not great, the patient's best interest will usually be served by thoracotomy, local excision, and immediate pathologic examination of the offending area. Additional surgery may then be carried out as conditions warrant.

SUMMARY

Lung lesions of indeterminate nature may occur in the practice of any physician, presenting as extensive diffuse lesions, local infiltrations, or isolated nodular disease. The diagnosis may be easily made in some cases, while other lesions require extensive and detailed study. A few may

defy every effort to find the true answer. Such lesions present an extremely interesting and intriguing group of problems, the final solution of which may tax our diagnostic skills to the utmost.

This paper was read at the meeting of the North Dakota State Medical Association, Fargo, North Dakota, May 6 to 9, 1961.

THE RADIOIODINE-LABELED ROSE bengal test is apparently the most useful single criterion for differentiating atresia of the extrahepatic bile ducts from intrahepatic conditions causing obstructive jaundice in infants. Fecal excretion of 10 per cent or more of the injected dose in seventy-two hours is diagnostic of obstructive jaundice and patent ducts; the upper limit with atresia is half this amount. Differentiation is essential, since isolated atresia of the extrahepatic bile ducts must be corrected within the first four weeks of life to avoid irreversible liver damage.

The radioactive rose bengal test is highly sensitive to such minor variations in degree of biliary obstruction as often exist in the two conditions. Conventional liver function tests are of little differential use, since tests of parenchymal function are negative in most infants with either condition. Moreover, in many infants with obstructive jaundice and patent extrahepatic ducts, stools are pale and duodenal fluid colorless for long periods; qualitative tests for urobilin, urobilinogen, and bilirubin are negative in the stool and duodenal fluid, and normal traces of urobilin and urobilinogen cannot be found in the urine.

Technics for obtaining quantitative stool specimens without urine contamination are cumbersome and may limit use of the test to large pediatric centers. Amount of radiation received is small and should not prevent use of the test whenever indicated. Radioiodine-labeled rose bengal was given intravenously to 3 infants without liver disorders, 5 with proved atresia of the extrahepatic bile ducts, and 7 with established obstructive jaundice and ductal patency. The day before injection, 3 drops of Lugol's solution was given to block the thyroid gland. Prepared radioiodine-rose bengal was diluted with nonradioactive rose bengal and saline to make 1 to 10 mg. of dye containing 1 μ C. of radioactive substance in a solution of 1 to 2 cc.

The healthy infants excreted 70 to 90 per cent of the injected dose in the stool and 4 to 5 per cent in the urine. All but 1 infant with atresia excreted 2.2 to 5 per cent of the injected dose in a seventy-two-hour stool collection and 30 to 47 per cent in the urine. The fifth infant was tested six weeks after surgical correction of atresia and had fecal excretion of 51 per cent. Similar results were obtained in a dog with surgical ligation of the common bile duct. In 7 infants with obstructive jaundice and patent extrahepatic ducts, fecal excretion varied greatly, being over 10.5 per cent in all cases. Peak fecal excretion was on the second day in all except constipated patients.

H. GHADIMI and A. SASS-KORTSAK: Evaluation of the radioactive rose-bengal test for the differential diagnosis of obstructive jaundice in infants. *New England J. Med.* 265:351-358, 1961.

Surgical Treatment of Deafness

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DURING THE last decade, new operations, stapes surgery and tympanoplasty, have been added to the field of otologic surgery. Stapes surgery was done in Europe as early as 1878 and 1890 by Kessel,¹ Miot² and, in this country, in 1892 and 1893 by Blake³ and Jack.⁴ The operation was abandoned, possibly because of inadequate results and complications. Rosen,⁵ in 1953, restarted stapes mobilization; since then, various technics⁶⁻⁸ have been introduced, with an increasing percentage of success.

Tympanoplasty was discovered by the methodical work of Zöllner^{9,10} and Wullstein.^{11,12} The purpose of tympanoplasty is the elimination of middle ear, or mastoid, disease and reconstruction of the sound conduction mechanism.

TYMPANOPLASTY

The basic physiologic principles of tympanoplasty are (1) transformation of the sound energy to the oval window and (2) protection of the round window. Transformation of the sound energy is done by the drum and the ossicular chain; the anatomic structure provides a lever and a hydraulic factor. The hydraulic factor is produced by the relation of the size of the tympanic membrane (55 sq. mm.) to the size of the stapes footplate (3.2 sq. mm.¹³) and is equal to 17:1. The lever factor is produced by the malleus and incus and is equal to 1.3:1. These two factors produce the transformer¹⁴ ratio of 22, which is equal to 26.8 decibels.

The round window in the normal ear is protected by the tympanic membrane. In the pathologic ear, perforations or absence of the tympanic membrane or ossicular chain exposes the round window to the direct effect of the sound energy. If both windows are stimulated at the same time, the equal sound energy cancels its effect on the cochlear fluid.

Indications for tympanoplasty are (1) chronic otitis media and complications of the chronic otitis, such as perforated tympanic membrane or damaged ossicular chain, and (2) chronic mastoiditis. Contraindications for tympanoplasty are

(1) inadequate cochlear reserve, (2) uncontrollable malfunction of the eustachian tube, and (3) complication of the chronic mastoiditis, such as lateral sinus thrombosis or brain abscess. Various nomenclatures have been suggested for the classification of tympanoplasty. The classification suggested by Wullstein¹¹ is presented in table 1.

Technics of Tympanoplasty. There are five recognized types of tympanoplasty. These will be described under their respective headings.

Type I. Myringoplasty, or type I, is done on patients in whom infection is confined to the middle ear and the drum is perforated. Surgery is done under local anesthesia; 2 per cent lidocaine (Xylocaine) with 1/50,000 epinephrine (Adrenalin) is used for anesthesia of the external auditory canal.

Surgery is performed with the operating microscope. First, the perforation and the middle ear mucosa are inspected. If the middle ear is healthy, the epithelium around the perforation, approximately 3 to 4 mm., is removed. If the perforation is very large, the epithelium of the external auditory canal is removed; a full-thickness skin graft is taken from the retroauricular area and used for grafting (figure 1). For small perforations, vein grafts are preferred because of easy adaptability and lack of complication.

After adjustment of the graft, slight pressure is applied on the graft by packing. This packing is removed in a week. Theoretically, as far as hearing is concerned, air-bone gap closure is expected. Wullstein^{11,12} prefers to inspect the attic and the antrum before grafting. This is not

TABLE 1
TYPES OF TYMPANOPLASTY

Type I	Plastic repair of drum with or without meatoantrotomy
Type II	Atticoantrotomy with plastic repair of drum
Type III	Total plastic repair, large graft
Type IV	Total plastic drum repair graft on promontory
Type V	Plastic operation and subsequent fenestration

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Fig. 1. Tympanoplasty I. Heavy line indicates graft placed over malleus.

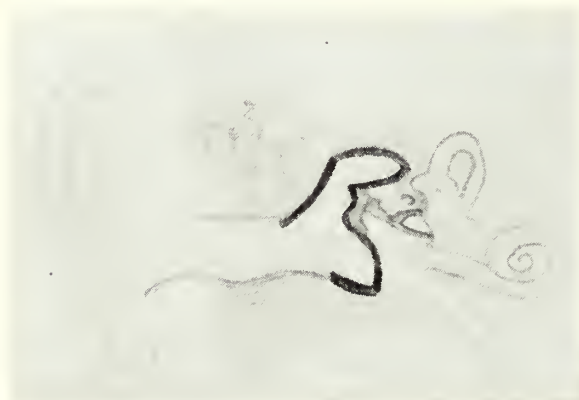


Fig. 2. Tympanoplasty II. Heavy line indicates position of graft over incus.

always necessary; it may be done in suspected cases to eliminate disease at these sites.

Type II. If the malleus is destroyed by the chronic otitis, this form of tympanoplasty is used. Endaural incision is used, and inspection of antrum and attic is done. If diseased tissue is present, it is removed and then grafting done, the graft being lowered to the level of the incus; thus, a slightly narrower middle ear is produced (figure 2). In grafting, the general rules as in type I are considered.

Type III. Usually, destruction of the malleus and the incus is present as a result of cholesteatoma or middle ear disease in the attic. In thoroughly cleansing the attic of disease, removal of bony bridge may be necessary. If the stapes is mobile and healthy, a graft is lowered to the level of the stapes (figure 3). If the stapes is embedded in the infected granulation tissue and fixed, a second operation may be necessary for the construction of the sound conductive system.

Theoretically, in tympanoplasty types II and

III, hearing level is 2.5 decibels below type I. In practice, this is rarely possible.

Types IV and V. If the stapes crura are destroyed, type IV operation is done (figure 4). In the presence of infection in the middle ear, tympanoplasty type V is done (figure 5), by fenestrating the semicircular canal. In these two operations, the transformation of the sound en-



Fig. 3. Tympanoplasty III. Heavy line indicates position of graft over stapes.

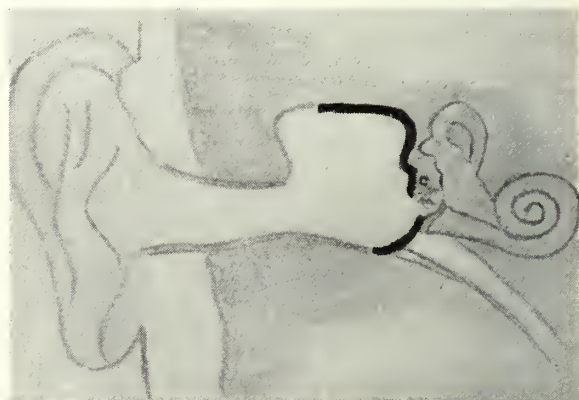


Fig. 4. Tympanoplasty IV. Heavy line indicates position of graft. Small hypotympanum is produced.



Fig. 5. Tympanoplasty V. Heavy line indicates graft placed over semicircular canal. Middle ear space is narrowed.

ergy to the oval window is omitted; only the protection of the round window is achieved.

Results. The largest group of patients had type I tympanoplasty (table 2). In 29 cases, serviceable hearing improvement was obtained; only 2 cases failed to gain adequate improvement. The second largest group of patients had the type III operation. Failure in 2 cases was caused by inadequate lowering of the graft, and in 1 case, refixation of the stapes occurred because of the scar tissue. Good results were obtained in 12 cases. No complication has been observed as a result of surgery. In 50 per cent of the type II, IV, and V cases, serviceable hearing was obtained.

Comment. Tympanoplasty types IV and V may be eliminated by converting these operations to tympanoplasty type III. In the presence of infection, reconstruction of the conductive system is executed in a second stage by removal of the footplate and vein grafting, with insertion of a polyethylene strut; 3 patients have been operated on by this method, with very good results. Since the introduction of constructive surgery of the middle ear, radical mastoidectomy has been eliminated.

STAPES SURGERY

Otosclerosis is a disease of the otic capsule. It involves the anterior crus in 70 per cent of cases. The footplate is completely fixed in 22 per cent of cases, and the posterior crus is fixed in 8 per cent of cases. In otosclerosis of the anterior crus, the footplate is ankylosed in various degrees.^{15,16}

Since the reintroduction of stapes mobilization by Rosen,⁵ various technics have been designed.^{6-8,17} These technics may be enumerated as stapes mobilization, crurotomy,⁶ stapedioplasty,⁷ mobilization of footplate, and stapedectomy with vein grafting.⁸

With stapes mobilization, the percentage of

TABLE 3
METHODS OF STAPES OPERATION

- I. Stapes mobilization
- II. Anterior or posterior crurotomy with mobilization of footplate
- III. Anterior-posterior crurotomy with mobilization of footplate and polyethylene tube strut
- IV. Stapedectomy vein graft

success has been reported¹⁷ to be as high as 26 per cent; later, in approximately 20 per cent of cases, the stapes reankyloses. Early results with stapedectomy vein grafting have been reportedly very successful.^{8,18} Air-bone closure for the 512-1024-2048 frequency range has been accepted as an index for evaluation of stapes surgery and has been obtained in 90 per cent of the cases.¹⁹

I believe a progressive approach is logical in stapes surgery. Each case must be carefully evaluated. Also, the type of the otosclerosis is an important factor; vascular otosclerosis is apt to reankylose in a short time. Stapedectomy interposition of graft usually will give the most lasting result.

Mobilization of the stapes should be reserved only for early avascular otosclerosis; if the anterior crus is fixed, then anterior crurotomy with mobilization of the footplate outside the otosclerosis focus should be done. Mobilization of the footplate was used in my early cases but was abandoned because of the complications. If the stapes footplate is fixed, stapedectomy vein grafting with the insertion of a polyethylene tube is done. The methods used are shown in table 3.

Technic of operation. The surgery is done under local anesthesia. Lidocaine (Xylocaine), 2 per cent, with 1/50,000 epinephrine (Adrenalin), solution is used. The canal is sterilized with tincture of methiolate. Using an operating microscope, a skin flap is elevated from the posterior wall of the external auditory canal, with 2 incisions starting close to the tympanic membrane at 6 and 12 o'clock positions. These two incisions are connected approximately 4 mm. from the tympanic membrane. The tympanic ring is elevated and the middle ear space is exposed. The chorda tympani is visualized and elevated. Usually, removal of the bony external auditory canal is necessary for visualization of the stapes and the footplate. At this stage, the middle ear structures are examined with higher magnification, 10 and 16, of the microscope. After seeing the round window, facial canal, stapes, and otosclerotic bone, the decision is made as to the type of surgery to be done. In early lesions, mobilization of the stapes; in localized avascular otosclerosis,

TABLE 2 RESULTS OF TYMPANOPLASTY IN 54 PATIENTS				
Type of operation	No. of cases	Improved 30 decibels	Improved 30-15 decibels	Improved 15-0 decibels
Tympanoplasty I without antrotomy	14	5	7	
Tympanoplasty I with antrotomy	17	7	8	2
Tympanoplasty II	2	1	1	
Tympanoplasty III	15	7	5	
Tympanoplasty IV	2	1		
Tympanoplasty V	4	1	1	
Total	54			

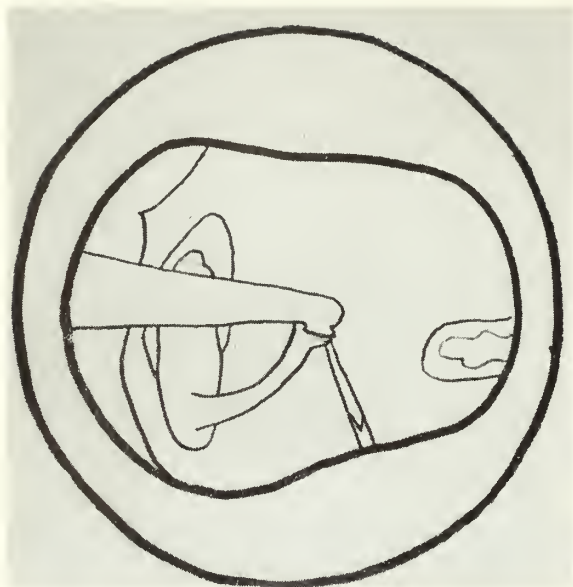


Fig. 6. Anterior crus removed. Figure shows mobilized portion of footplate.

crurotomy (figure 6) and mobilization of the footplate (figure 7); and in advanced cases, stapedectomy vein grafting is done (figure 8). For the latter, the stapes tendon is cut and the incudostapedial joint disconnected and the mucosa of the portion of the bony facial canal over the promontory is denuded. Then, with the drill, the promontory is lowered. If the footplate is thin and the center bluish, a fine pick is inserted and

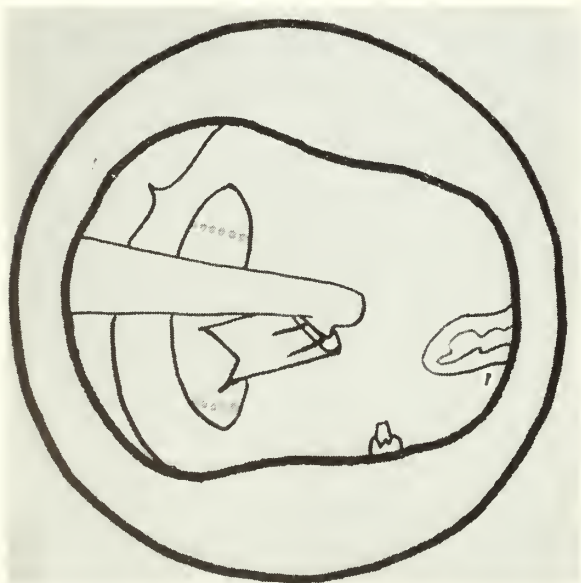


Fig. 7. Stapes removed. Line shows central portion of mobilized footplate. Polyethylene tube is placed over mobilized footplate.

the footplate carefully fractured and removed in fragments. The vein graft taken from the forearm or hand is thinned and, with the intima facing the labyrinth, placed over the oval window. A polyethylene tube No. 90 is placed over the oval window, and the distal end is fitted to the lenticular process of the incus by slightly lifting the lenticular process. A very small gelatin sponge (Gelfoam) soaked with penicillin and cortisone is placed over the lenticular process of the incus. Then the tympanic membrane is placed on its normal groove. Patients are kept in bed two days, with the head turned slightly to the unoperated side. Antibiotics are administered for five days. Postoperative reactions are mild. Hearing improves in the first week, reach-

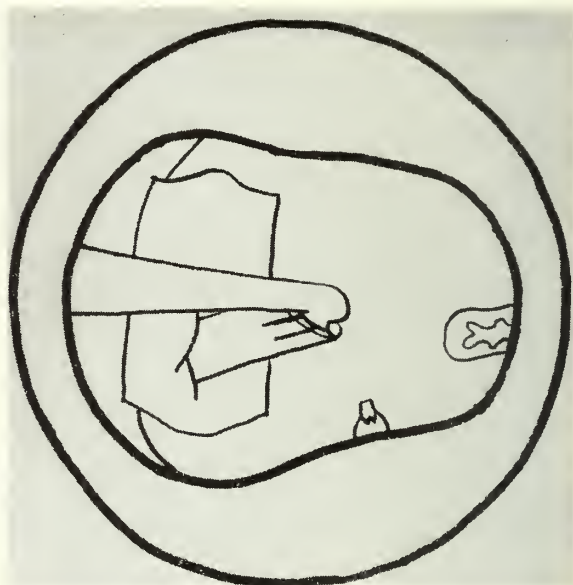


Fig. 8. Stapes removed. Vein graft is placed over oval window. Polyethylene tube is placed on vein graft.

ing its peak in the third week. The improvement for high tones may continue as long as six months.¹⁹

Results. The results of various technics are shown in table 4. The best results are obtained with stapedectomy and vein grafting. In spite of the very close anatomic relation,²⁰ the distance of the utricle from the oval window is 0.5 mm. and from the sacculus, 1 mm. This has been the safest method without any complication.

Complications. Infection was observed in 1 patient one week postoperatively; perforation of the tympanic membrane occurred in 1 case and was repaired by myringoplasty. Facial weakness developed in 1 case during the extraction of a very thick footplate but cleared in three weeks.

TABLE 4
RESULTS OF STAPES SURGERY

Type of operation	No. of cases	Improved 15-30 decibels	Air-bone gap closure
Stapes mobilization	10	7 (70%)	3 (30%)
Anterior crurotomy with mobilization of footplate	3		3 (100%)
Mobilization of footplate with polyethylene tube strut	52	42 (80%)	40 (70%)
Stapedectomy vein graft	61	57 (93%)	54 (89%)
Total	126		

Delayed cochlear damage has been reported in as much as 2 per cent of the cases;^{14,19,21,22} this was seen in 3 patients. Diagnostic tympanotomy revealed fistula formation of the footplate²³ in 2 cases, in 1 of which it was attributed to an allergy.

Acute cochlear damage occurred in 1 patient; hearing dropped 10 decibels for bone conduc-

tion. This case is thought to present an anomaly of the membranous labyrinth.

Comment. Stapedectomy vein grafting, in spite of technical difficulty, is the safest stapes operation. No delayed cochlear damage has occurred in this group. The polyethylene tube has been tolerated well by the middle ear. In spite of experimental findings in animals,²⁴ vein graft is well tolerated. No progressive cochlear damage has been reported.

Taste disturbance produced by severing the chorda tympani may last a few months. Avoidance of this is preferred. The only unanswered question at the present time is, what will be the effect of elimination of the stapes reflex during stapedectomy, although no cochlear deterioration has been reported since the introduction of stapedectomy vein grafting.⁸

Stapes surgery in its present form has replaced fenestration for the surgical treatment of otosclerotic deafness.

This paper was read at the meeting of the North Dakota State Medical Association, Fargo, North Dakota, May 6 to 9, 1961.

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Thomas Ziskin

A Personal Tribute

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FEW PHYSICIANS have been as modest, calm, temperate, dedicated to the practice of medicine, and considerate of others as Tom Ziskin. He was born in Grand Forks, North Dakota, on November 29, 1888. He attended the public schools in Grand Forks and was valedictorian at his high school class commencement.

In 1905, Tom entered the University of North Dakota; two years later, he transferred to the University of Minnesota where, in 1911, he received the degree of doctor of medicine. The next year he entered private practice in Minneapolis and for three years was also part-time assistant city physician. From 1917 to 1921, he was medical inspector in the Minneapolis Health Department.

During 1918-19, he served as first lieutenant in the medical corps of the United States Army. He was appointed consultant in diseases of the heart in 1921 and continued in that capacity with the United States Veterans Administration until 1945. From 1919 to 1927, he was clinical instructor in medicine at the University of Minnesota Medical School, then assistant professor of medicine until his retirement.

Dr. Ziskin was a diplomate of the American Board of Internal Medicine and was active in his county, state, and national medical associations. Many other organizations were honored by his membership, including the Minneapolis and Minnesota Societies of Internal Medicine, the Minnesota Pathological Society, the Central Society for Clinical Research, the American Heart Association, and the American College of Physicians. His recognition as a scientist was

indicated by election to membership in Sigma Xi.

He took an active part in the Jewish Family Service Association, served on its board of directors, and was secretary of that board from 1925 to 1943. He belonged to Phi Delta Epsilon Fraternity and was an active member of Temple Israel.

He was so retiring that few of his medical associates knew he was both a musician and an artist. While a medical student at the University, he played in the band, wrote music, and had several of his musical compositions published.

Few of his colleagues knew that he had been honored by Beth Israel Hospital, Newark, New Jersey. His picture is displayed in the hospital gallery among others of the foremost heart specialists in this country.

During World War II, from 1944 to 1946, he served as major in the medical corps, AUS.

In the late winter of 1921, Dr. F. E. Harrington, commissioner of health of the city of Minneapolis, requested that a medical staff be organized for the Lymanhurst Hospital and School, which was to be opened in May. Dr. Ziskin was one of the first persons to be invited to join this staff. Staff meetings were held every two weeks; as director of cardiology, Dr. Ziskin almost never missed a meeting and always responded to requests to present papers before the staff. For example, in 1921 he read a paper entitled, "Cardiac Signs in Early Pulmonary Tuberculosis in Children;" in 1923, "The Heart and Tuberculosis;" in 1924, "Vital Capacity as a Functional Test for Heart Diseases;" in 1925, "Investiga-

tions on Development and Size of the Heart in Children by the Teleroentgen Method;" and, in 1929, "The Spirit of Research of Sir James McKenzie." The paper on "Development and Size of the Heart" was a result of extensive and excellent research and was published in the December 1925 issue of *The American Journal of Diseases of Children*. In 1932, he published an article on "Significance of the Q Wave in the Electrocardiogram," and, in 1949, he wrote on "Observations on the Heart in Epilepsy."

Dr. Ziskin's work on the staff added greatly to the significant contribution made by Lymanhurst in regard to knowledge of tuberculosis among children.

On October 16, 1924, Dr. Ziskin was married to Miss Tekla David of Columbus, Ohio. Throughout the years, Mrs. Ziskin was of immense help to her husband in all his work.

When THE JOURNAL-LANCET was acquired by the present publishers, a request was made that an editorial board be organized covering the various aspects of work of the medical profession. Tom Ziskin was immediately chosen to direct work in cardiology, which included reading all such papers submitted and determining their suitability for publication. He was also elected secretary of the editorial board and served in that capacity from 1930 to the end of his life. He seldom missed an editorial board meeting and throughout the years was an ardent worker for the journal.

In 1961 he received a certificate testifying as to his fifty years of practice of medicine in Minnesota from the State Medical Association.

On July 12, 1958, Dr. Ziskin fell and sustained a hip fracture. He was admitted to the Mount

Sinai Hospital where a good therapeutic result was obtained. The admission examination also revealed a pulmonary lesion which was treated successfully. Although he did some work for awhile, he never completely regained his strength. He died on November 18, 1961, from an acute infection complicating diabetes.

As a part of a beautiful tribute, Rabbi Albert G. Minda said, "He communicated through his own heart with the heart of his patient, who saw in him not only a man of science but an understanding and sympathetic friend, one who was trying to heal in both the physical and spiritual sense. Regardless of his patients' status—economic, social, racial—Tom was the dedicated servant of his calling, dedicated to bring relief to and promote life in those who called upon his richly endowed talents and skills."

Since 1920, I have worked closely with Dr. Ziskin, not only in private practice but also through the medical staffs of Lymanhurst Hospital and School, the editorial board of THE JOURNAL-LANCET, and other organizations. On all occasions he was calm and retiring and manifested excellent judgment. He was soft spoken and never verbose. He was honest, truthful, trustworthy in every respect, and thoroughly ethical in the practice of medicine. During this period of more than forty years, I never heard him express anything but praise for his fellow physicians, individually and collectively. It was an honor, a privilege, and an uplifting experience to work with Tom Ziskin. In his quiet way, he had a fine influence on all who came in contact with him. His life and work established goals which physicians young and old should strive to attain.

Book Reviews . . .

Surgery: A Concise Guide to Clinical Practice

GEORGE L. NARDI, M.D., and GEORGE D. ZUIDEMA, M.D., editors, 1961. Boston: Little, Brown & Co. 1,034 pages. Paperback. Illustrated. \$8.50.

This book is simultaneously surprising and pleasing. It is a part of a bold, new venture in medical publishing: paperback edition of basic texts at low cost, with the promise that new, up-to-date editions will be forthcoming.

Surgery: A Concise Guide to Clinical Practice accomplishes its stated purposes. It is concise yet comprehensive, an excellent guide to clinical surgery, as timely as a current journal, and as basically sound as the selected references given at the end of each section. In 1,034 compact pages, the book presents complete coverage of general and special surgery plus several interesting "extras."

The popularity which we predict for this publication will be due largely to the ability of the authors to handle a semioutline, economical style in such a manner that reading remains interesting and does not offend. We suspect that this was accomplished only by "taking time to be brief," to paraphrase Voltaire. Unfortunately, a small minority of the 23 authors, obviously straining to be brief, have produced nothing better than a syllabus for third-year medical students. Certain short sections of the book will annoy the reader, to say nothing of the English department of the author's university, if the reader indeed is willing to struggle through the maze of incomplete sentences and unconnected thoughts. We hasten to add that the few deficiencies in style which do exist stand out like a sore thumb which has been bandaged in forced hyperextension, simply because of the excellence of the abbreviated style in the book as a whole. One can afford to overlook these few deficiencies, at least in the first edition.

The authors have avoided discussion of surgical technique in a few places where such discussion seems to be in order. The authors did have a mandate to be brief and this is not an atlas, but we believe that a guide to the clinical practice of surgery cannot slough off its obligation to comment to some extent on currently acceptable technique. Again, we hasten to add that this sin of omission is limited to a few spots in an otherwise excellent treatise which does fulfill its obligations, including those relative to technique.

The publishers have done their job well. The binding of 1,034 pages in paperback form must be good if one expects the pages to stay in place with hard usage. Our copy has passed a tough first test with a perfect score. In deliberately seeking typographic errors in this book, replete with tables, charts, and abbreviations, we came away almost empty-handed, although line 7 on page 489, for example, did not escape our bifocal scrutiny. The black and white illustrations are clear, helpful, and quite appropriate to the format. A spot-check of the index scored well. The use of key references instead of complete bibliographies is to be highly commended—the references thus become meaningful.

This book will not be the most attractive volume on the library shelf, but it will gather no dust. This is a real bargain at \$8.50. The man in training and the active

practitioner interested in the general aspects of surgery will find it a text worthy of reading and study. The limited specialist will use this paperback as a handy reference when he wishes to refresh his knowledge of problems not directly within his scope, provided perusal of the section dealing with his specialty is acceptable to him within the limitations imposed by the definition "a concise guide."

DAVID P. ANDERSON, M.D.
Austin, Minnesota

Toward the Diagnosis of Congenital Heart Disease

W. CARLETON WHITESIDE, M.D., 1960. Springfield, Ill.: Charles C Thomas. 85 pages. \$4.50.

This book has no illustrations, 2 tables, no index, and no bibliography. There are scattered historical quotations, the source of some not given, and scattered numerical data which are unexplained.

In each of the 37 chapters are listed 7 to 136 items, each approximately 15 words in length. These are purported to be aphorisms, but the nuggets can be categorized as follows: (1) patently false, as "... a thrombosis in any artery of the body will cause hypertension in varying degrees" (page 5, item 12); (2) idiomatic, as "'Bird-like' movements of patients are seen in thyrotoxic heart disease" (page 9, item 51); (3) unintelligible, as "Collaterals prolong life; they are 'safety valves' for a time, but help in a diagnosis if observed during examination. Varicose veins are frequently due to cardiac obstruction and not from standing" (page 11, item 69) and "Anoxia is a concept of pathologic physiology" (page 11, item 74).

The author is so fascinated with aphorisms that he cites several on rheumatic and coronary artery diseases despite his announced purpose to aid the reader in the diagnosis of congenital heart disease; these aphorisms are no better than those concerning his principal subject.

Much can be said for aphorisms in medicine, and as an art form, it should be encouraged. This volume should stimulate others to fashion better ones.

Whiteside's statements might be used by the medical instructor pressed for time as the false entries in a true-and-false test. He will find a few true ones here and solicit others from reputable sources.

The book is not recommended for purchase or reading by any member of the profession at any level.

WILLIAM BRADLEY MARTIN, M.D.
Duluth, Minnesota

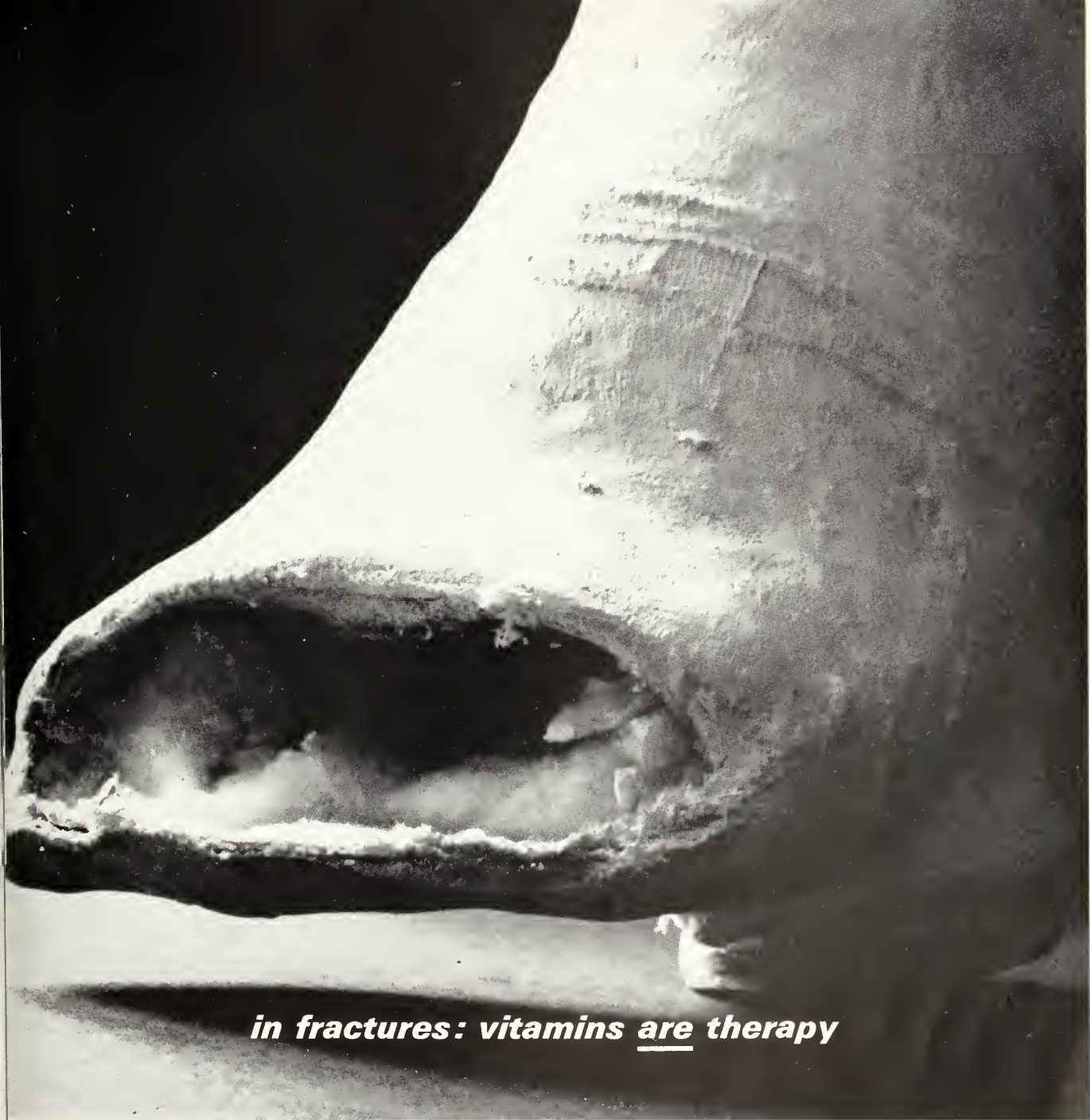
The Human Blood Proteins

PROF. FERDINAND WUHRMANN, M.D., and CHARLIE WUNDERLY, Ph.D., 1960. New York: Grune & Stratton. 496 pages. Illustrated. \$15.75.

There are, no doubt, moments in the busy work-a-day life of every practicing physician when he raises his eyes above the level of the work immediately before him and wistfully looks to the distant horizons of investigative medicine. We never lose this longing to pursue the Art.

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(Continued on page 18A)



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BOOK REVIEWS

(Continued from page 42)

provides the thoughtful clinician with a lucid understanding of the blood proteins, and it is loaded with useful concepts to take to the bedside.

The book is beautifully written, and its order of exposition is carefully planned. After a thorough review of the nature of normal blood proteins and a description of the various physicochemical and immunologic methods by which they are studied, the authors present the monumental fifth chapter, which discusses their clinical significance. Here are passed in review what the authors call "reaction constellations." These are depictions of all the disease states in which the various blood proteins play a significant role, each with an itemized list of the various laboratory protein determinations pertinent to it. This chapter further combines in articulate pattern what would otherwise be a befuddling array of laboratory tests, explaining their interrelationships and the vagaries of their interpretation.

After a discussion of the dys- and paraproteinemias, the book concludes with a consideration of the formation and synthesis of the blood proteins. This portion of the book is but a brief exposé of a highly controversial subject, treating it lightly but provocatively.

The Human Blood Proteins towers in its erudition and mastery. Within its pages are to be found nuggets of understanding which fill many a void in ambulant knowledge. To mention just a few as examples—we learn here something really concrete about the A/G ratio; about the difference between the much-mentioned "direct" and "indirect" van den Bergh reaction; and about the intricacies of protein-binding.

The bibliography is quite complete and is conveniently listed piecemeal at the bottom of the pages containing the references.

Anyone desiring a predigested, cookbook type of book which will give helpful hints with little effort is cautioned to stay clear of this work. *The Human Blood Proteins* requires attentive and somewhat laborious reading. But to anyone with a sincere affection for knowledge—knowledge which must be dug out if necessary—the reading of this book will be permanently rewarding.

CAMILLO V. BOLOGNA, M.D.
Hibbing, Minnesota

The Cry for Help

NORMAN L. FARBEROW, PH.D., and EDWIN S. SHNEIDMAN, PH.D., editors, 1961. New York: McGraw-Hill. 398 pages. \$9.95.

This book, which focuses on the prevention and treatment of suicide, makes a significant contribution to the understanding of this puzzling, frightening, and often guilt-producing phenomenon, which is not confined to any age group. The editors and some contributors are members of the staff of the Los Angeles Suicide Prevention Center (LASPC).

Part I of the book presents a brief overview of some of the community attempts now in existence, both in this country and abroad, which are aimed at prevention. A detailed description of the LASPC focuses on its relationship to other community agencies and on current findings produced in fulfilling the 3 basic functions of the center—saving human lives, establishing LASPC as a public health agency, and research. Some very practical results are already in evidence, the most useful, perhaps, being a consideration of what is involved in assessing self-destruction potentials, particularly in the

quick evaluation of an emergency situation. Comparison between actually committed and attempted suicides confirms some and dispels other assumptions generally thought to be operating in self-destruction. For example, findings clearly point to the danger of repetition after an unsuccessful attempt during that period which is often characterized by resumption of activities and by apparent return to well-being. This, of course, raises questions about the current practices of release from hospitals and other protective situations. Implications for follow-up care are self-evident, then.

Part II consists of papers by different contributors, each describing a particular theoretic approach to the dynamics of self-destruction. Represented are the points of view of psychoanalysis—Adler, Horney, Jung, and Sullivan—and of the personal construct and nondirective approaches. Each author applies his concepts to a case history and indicates the nature of treatment that would logically follow from his respective theoretic context.

While the work is addressed primarily to mental health personnel and other community caretakers, troubled family members will also find much that is of value to them. Physicians, psychotherapists, ministers, nurses, hospital personnel, social workers, police officers, even coroners, and others who are apt to be in contact with potentially suicidal persons can learn a great deal. Most important, it sharpens sensitivity in listening and arouses community conscience to respond to the "cry for help."

II. ETTA SALOSHIN, PH.D.
Minneapolis

Performance Capacity

HARRY SPECTOR, JOSEF BROZEK, and MARTIN S. PETERSON, editors, 1961. Chicago: Department of Army, Research and Development Command, Quartermaster Food and Container Institute for the Armed Forces. 257 pages. Illustrated.

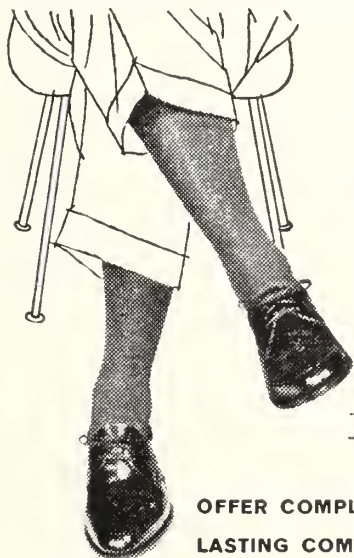
This volume, consisting of 38 articles by various authors, gives a good cross section of the fundamental aspects of fitness testing. The articles are grouped into the following sections: (1) body functions involved in work and their use to predict performance capacity, (2) application of standard work tests, (3) effect of environmental stresses on performance capacity, and (4) general discussion. The main emphasis is on cardiovascular-respiratory functions (H. L. Taylor, B. Balke, F. N. Craig, and R. R. Buskirk), but the digestive system (E. S. Nasset), the adrenal system (F. Elmadjian and I. Gray), and psychomotor functions (J. Brozek) are also discussed. Most of the fitness tests involve a high level of performance and are designed mainly for military personnel and not for clinical application. For fitness testing of patients, particularly older patients, a much lower level of performance would be needed. However, some of the information in the volume is potentially useful for clinical application.

The electrocardiographic exercise test, which is widely used clinically but rarely in fitness tests of military personnel or athletes, is not included, and this is consistent with the general character of the book. The environmental stresses discussed are mainly heat and cold.

Kimeldorf found that the pattern of activity performance of rodents after exposure to 300 to 1,000 r is very similar to the sequence of events in man following exposure to radiation levels comparable in the resulting mortality. Elmadjian's article, "The Sympathico-Adrenal System," is one of the longest and best documented. Variations in adrenalin and noradrenalin excretion are demonstrated in various emotional states. Noradrenalin

(Continued on page 20A)

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BOOK REVIEWS

(Continued from page 18A)

excretion is increased in active, aggressive emotional displays and adrenalin, in cases of tense and anxious but passive display.

The effect of age is not discussed except in J. Brozek's epilogue, which also gives an excellent summary of the effects of nutrition, drugs, fatigue, heat and cold, and some diseases, with a bibliography of 58 references.

The volume contains much condensed information of value for sport-physicians, cardiologists, neurologists, and psychiatrists.

ERNST SIMONSON, M.D.
Minneapolis

The Human Adrenal Gland

LOUIS J. SOFFER, M.D., RALPH L. DORFMAN, PH.D., and
J. LESTER GABRILOVE, M.D., 1961. Philadelphia: Lea
& Febiger. 591 pages. Illustrated. \$18.50.

The timely subject of adrenal anatomy, physiology, and chemistry, and the broad therapeutic applications of recent knowledge in this field herald an exciting new era in clinical medicine, enhancing the well-being and longevity of patients far beyond the sphere of mere dysfunctional maladies of this enigmatic gland. The busy clinician, however, finds it most difficult to keep his head above water in the vast, often turbulent, sea of literature available in this field alone. In this regard, Soffer's new text fulfills the urgent need for a reliable authoritative volume encompassing all practical considerations and most of the important theoretic aspects relative to clinical medicine, serving the internist and general practitioner alike.

It would be naive to imply that pathologic physiology of the adrenal gland is less than highly complex, but the authors of this text have gone a long way toward simplification of context without undue compromise of accuracy. Several thousand references attest to the latter statement.

All adrenal hormones, including medullary and cortical derivatives, together with synthetic analogues, are thoroughly reviewed.

The illustrations, style, and format make for pleasant reading by the hour.

E. A. HAUNZ, M.D.
Grand Forks

Radiation Therapy of Early Prostatic Cancer

R. H. FLOCKS, M.D., and D. A. CULP, M.D., 1960. Springfield, Ill.: Charles C Thomas. 73 pp. Illustrated. \$4.50.

The authors have developed the technic of treatment of inoperable carcinoma of the prostate with injections of radioactive gold (Au^{198}) directly into the tumor.

The patients selected had tumors which had spread beyond the confines of the prostate and into the lymphatics but had not given rise to clinically evident distant metastases. About 40 per cent of the patients had metastases in pelvic lymph nodes, which were treated with surgical excision followed by local infiltration with radioactive gold.

In an interesting review of the literature regarding the use of radiation therapy for prostatic carcinoma, the authors emphasize the radioresistance of these tumors, which necessitates a high local dose to the tumor. This can be achieved by careful attention to technical details, with injection of small volumes of the colloidal solution of radioactive gold of a concentration of 20 to 30 mc. per milliliter. Each fascial compartment is injected separately with about 0.5 ml. after opening the bladder

BOOK REVIEWS

through the suprapubic approach or by exposing the prostate through an open perineal approach. Closed perineal and transrectal techniques have also been explored. The total volume of radioactive gold injected seldom exceeds 2 to 3 ml.

Excellent tumor regression with relief of symptoms combined with a low incidence of complications and a five-year survival rate of 43 per cent in 135 patients was achieved.

This book should stimulate the cooperative efforts of urologists and radiologists to attempts at reproducing these favorable results in a condition which is often regarded as hopeless and therefore subjected to palliative measures only.

The contents of the book are presented in a clear and logical form. The illustrations are good and the over-all appearance attractive.

H. VERMUND, M.D.
Madison, Wisconsin

Henry Stanley Plummer—A Diversified Genius

FREDRICK A. WILLIUS, M.D., 1960. Springfield, Ill.: Charles C Thomas. 71 pages. \$4.50.

This small book will be greatly appreciated by those who knew Dr. Plummer personally, and it is a most welcome effort on the part of the author, Dr. Fredrick A. Willius, emeritus cardiologist of the Mayo Clinic, who knows whereof he writes. It is to be hoped that the work will remind past, present, and future members of the staff of the Mayo Clinic how much they owe to this man who was truly a genius and that it will help those who did not know him to recognize how far his greatness served to make the Mayo Clinic great.

JOHN S. LUNDY, M.D.
Chicago

Science in Everyday Things

WILLIAM C. VERGARA, 1960. New York: Harper & Brothers. 308 pages. Illustrated. \$3.95.

With interest in science at so high a level, this book is of value to those who are in a position to guide young people along the paths of scientific inquiry. It is neither a textbook nor an occupational guide but rather an aid to parents and teachers of children with inquiring minds. In addition, the questions and answers are valuable to the preparation of material for nonprofessional groups interested in science and its applications.

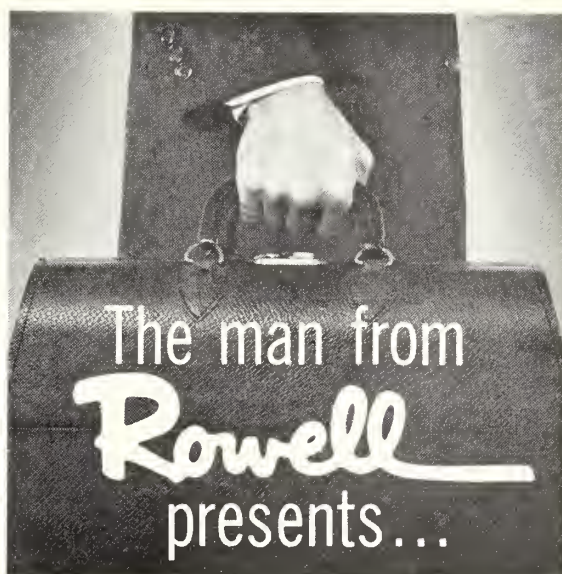
Management of Fractures, Dislocations and Sprains

H. EARLE CONWELL, M.D., and FRED C. REYNOLDS, M.D., seventh edition, 1961. St. Louis: C. V. Mosby. 1,129 pages. Illustrated. \$27.00.

The seventh edition follows a succession of very favorably accepted revisions. To consider, however, that this text is an extensive revision of former editions would be unrealistic. The photographs are in a large part reproductions of those used in earlier volumes, while many portions of the text remain unchanged.

There is some discussion of additions to our clinical armamentarium of fracture treatment, but there are some presently popular techniques that have not been analyzed. These procedures might deserve mention even though their value may not be universally accepted. The reader might appreciate the mechanics and applications of

(Continued on page 22A)



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BOOK REVIEWS

(Continued from page 21A)

such procedures as sliding nail and shaft fixation for intracapsular fractures of the hip, contact compression plates, and the various forms of threaded wire fixation.

Other additions serve a useful purpose by keeping the reader informed of current fundamental concepts in the basic science field. More thorough consideration of the subjects of fracture healing and fat emboli have been included.

The presentation of jaw and facial injuries is extremely thorough. The inclusion of soft tissue injuries to the hand is welcome in a trauma text and provides a broader knowledge of common hand problems to the reader.

Former editions have served as an academic background in trauma for many students. Although it is somewhat difficult to recommend this text to those who now own the preceding volume, it should still maintain its position as a reference available in larger libraries.

WALTER INDECK, M.D.
Minneapolis

Control of Ovulation

CLAUDE A. VILLEE, *editor*, 1961. New York: Pergamon Press. 251 pages. Illustrated. \$10.00.

This book is a collection of 12 papers read and discussed at a conference in ovulation, which was held in Dedham, Massachusetts, in 1960.

Although the subject material makes fascinating reading, it is primarily of interest to researchers in the field of endocrinology, chemistry, physiology, anatomy, and other related sciences. It is of little benefit to the practitioner concerned with actual patient care. It would not be recommended except as a reference book on recent advances in ovulation.

FRED A. LYON, M.D.
Minneapolis

Clinicopathological Conferences of the Massachusetts General Hospital: Selected Medical Cases

BENJAMIN CASTLEMAN, M.D., and H. ROBERT DUDLEY, JR., M.D., *editors*, 1960. Boston: Little, Brown & Co. 289 pages. Illustrated. \$12.50.

In 1900, Walter B. Cannon, then a student at Harvard Medical School, suggested the use of the case system method in medical education.¹ He had been impressed by the enthusiasm with which students at the Harvard Law School had greeted this approach to teaching, which had been practiced for some twenty-five years previously in the Law School. Cannon suggested, "to these cases the students can bring all their knowledge of anatomy, physiology, pathology, and therapeutics, and these subjects which are now more like separate packets in the mind than related parts of a single system take on a new importance and interest. The students thus fix their knowledge by unifying it."² Shortly thereafter, Dr. Richard Cabot, who was to become so intimately associated with the Clinical Pathological Conferences, began to use this method of teaching both in his office and at the Harvard Medical School. Soon transcripts of the CPC were being sent through all parts of Europe, and, by 1924, the same discussions began to be published in the *Boston Medical and Surgical Journal* which was later to become the *New England Journal of Medicine*.

Since 1924, over 3,000 case records have appeared in the journal. In response to multiple requests for a compilation of selected CPC transcripts, the present editors have collected 50 cases which deal with significant prob-

BOOK REVIEWS

lems in the field of internal medicine. These cases cover the period of 1936-1959.

Not only are the cases varied, but the discussions present the deductive reasoning and knowledge of some of the most important men in American medicine. Herein lies one of the significant contributions of this compilation. We are able to follow the logical reasoning and thought of men whose contributions to medicine have been extensive. The discussions are complete and interestingly presented. When necessary, addenda to the discussions appear and serve to complement and, in some cases, bring up-to-date the current medical thought on the particular subject discussed.

The book is well edited and printing is clear. The book appears durable. The subject index is adequate and includes a list of the various contributors.

This book will be of particular value to the internist and to the student of medicine, not only for its practical teaching value but from a historic viewpoint. In the future, the editors plan to compile other Clinical Pathological Conferences which more directly relate to other aspects of the field of medicine.

1. CANNON, W. B.: The Case method of teaching systematic medicine. Boston Med. & Surg. J. 142:31, 1900.
2. CANNON, W. B.: The Case system in medicine. Boston Med. & Surg. J. 142:564, 1900.

ROBERT O. MULHAUSEN, M.D.

Minneapolis

Histopathologic Effects of Local Anesthetic Drugs

PHILIP PIZZOLATO, M.D., 1961. Springfield, Ill.: Charles C Thomas. 100 pages. Illustrated. \$5.50.

This book, printed on good paper, is profusely illustrated to show the histopathologic effects of local anesthetic drugs. There is an index, and 97 references are listed. The book comes out at a particularly appropriate time, since the swing away from local anesthetics has been considerable and it is about time for the trend to swing in the opposite direction. The book also is very important because there is much good to be said about local anesthetics and they are not used enough today.

JOHN S. LUNDY, M.D.

Chicago

Gynecologic Endocrinology

EDWARD A. GRABER, M.D., 1961. Philadelphia: J. B. Lippincott. 218 pages. \$7.50.

Common endocrine problems frequently encountered in gynecologic practice are concisely reviewed in this book. Each short chapter is limited to specific disease and syndrome complexes with subheadings easily divided into symptoms, physical findings, and therapy. Also included are laboratory tests of value in deciding on the differential diagnosis, and what is more, a clear guide in the interpretations of these laboratory results and their normal values.

The real value of the book lies in the simplicity with which the complicated array of gynecologic endocrinopathies are described. The bibliography which is included is in itself a ready reference manual and deserves careful perusal by the interested reader.

Included in the book are excellent sections on infertility, the role of the thyroid and adrenal gland in gynecology, and the endocrine problems associated with pregnancy. The volume should be helpful to all practitioners seeing and treating the female patient.

FRED A. LYON, M.D.

Minneapolis

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Gynecology, Office & Operative, Two Weeks, April 9

Vaginal Approach to Pelvic Surgery, One Week, March 26

Obstetrics, General & Surgical, Two Weeks, March 12

Pain Relief in Childbirth, 3 Days, March 7

Proctoscopy & Sigmoidoscopy, One Week, March 26

Treatment of Varicose Veins, One Week, March 26

Basic Internal Medicine, Two Weeks, March 26

Basic Electrocardiography, One Week, March 19

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Surgery of Hernia, 3 Days, March 15

Urology, Two Weeks, April 2

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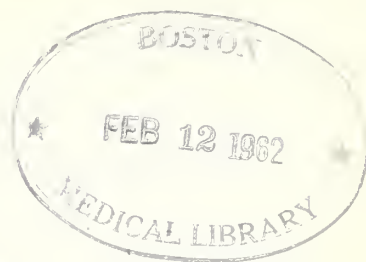
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EDITOR'S NOTE: *The papers appearing in this issue were read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, Minnesota, January 27, 1962, and have been selected from GEORGE E. FAHR FESTSCHRIFT, Lancet Publications, 1962.*

The Pathophysiology of Lung Edema A Physical and Physicochemical Problem

MAURICE B. VISSCHER, M.D.

Minneapolis

IT IS A PLEASURE and a privilege for me to contribute to a group of papers honoring Professor George Fahr. He, more than any other person, introduced me, when I was his student, to the potentialities of application of the exact physical sciences to the practical problems of medicine. He first intrigued my fancy concerning the basic simplicity, but ultimate complexity, of closed hydraulic systems in which the working efficiency of the pump determined the hydrostatic pressure relations in all segments of the circuit. As an intern on his service at the Minneapolis General Hospital, I learned, too, that a rigid medical scientist could be a most sensitive human being in his attitudes toward, and actions with, suffering patients. I learned that there is no incompatibility between human sympathy and the scientific method. I suspect very strongly that persons who bemoan the rising tide of importance of physics and chemistry in medicine and fear a decline of emphasis upon the human relationship, the patient-physician relationship, are themselves not adequate to the performance of both requirements. Surely, as

the man we honor today has shown in his own life and work, there is no inherent bar to being at once a scientist and a physician.

EDEMA OF THE LUNG

Lung edema can be considered simply as a state in which there is an abnormal accumulation of water in some or all parts of the lung. Theoretically, there can be intracellular, interstitial, or intraalveolar accumulations of water in edema of the lung. Little is known about intracellular edema, however, and it will not be considered in this paper. Interstitial and intraalveolar edema are apparently parts or stages of a single process and will be considered together. By way of justification for a reconsideration of the problem, it may be noted that recent work has indicated that two mechanisms, not previously considered seriously as causative factors, now appear to add to the list of possible causes of lung edema which must be considered by the clinician dealing with this pathophysiologic process.

As we pointed out in a comprehensive review in 1956, lung edema production can be considered to be fundamentally a situation in which the rate of water movement out of the lung capillaries exceeds the rate of return directly through the capillary wall or via the lymphatic drainage.

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Water movement across the capillary endothelium occurs by virtue of the fact that the endothelium is permeable to water. The rates of movement in the two directions depend upon the physicochemical activity of the water in the internal and external compartments and the effective permeable area of the membrane in the case of any movement other than that which might be caused by local electrical forces. Since we know nothing about local electro-osmotic circuits in lung capillary walls, we shall not consider them except to point out that their possible occurrence should be borne in mind and that it is easily conceivable that some unexplained phenomena might be due to them.

The activity of water in solutions can be measured in a variety of ways: freezing point depression, osmotic pressure, vapor tension, and related measurements. The activity depends upon temperature and pressure as well as upon its effective mol fraction in a solution. The differences in rates of movement of water in directional flux depend upon the differences in activities in opposing compartments and upon membrane permittivity:

$$F_{\text{out}} - F_{\text{in}} = F_{\text{net}} \quad (1)$$

$$F_{\text{out}} = P A_{\text{H}_2\text{O plasma}} \quad (2)$$

$$F_{\text{in}} = P A_{\text{H}_2\text{O interstitial}} \quad (3)$$

$$F_{\text{net}} = P (A_{\text{H}_2\text{O}_p} - A_{\text{H}_2\text{O}_i}) \quad (4)$$

where P is the permittivity to water at any particular time and A is the activity of the water. P will be dependent upon pore size and numbers in a porous membrane or upon phase distribution and phase thickness in a continuous phase barrier system. A is dependent upon molar concentrations of all solutes, including both crystalloids and colloids, as well as upon hydrostatic pressure and temperature.

Among the known important variables in A , the colloid osmotic pressures and the hydrostatic pressures are the determining ones. It may be noted that A depends also upon the characteristics that determine P in a porous membrane, because pore size determines which solute particles will exert osmotic pressure.

PHYSICOCHEMICAL VARIABLES

It is my main purpose in this paper to analyze the actual physiologic variables which determine and alter the quantities A and P in the genesis of lung edema. Students of physiology are wont

to complain these days about the increasing complexity of physiologic science. I hope to show that, in reality, increasing knowledge can result in simplification of the conceptual frame upon which we can hang individual facts, which without such coordination would pose impossible problems in memory and understanding.

Variations in the quantity $A_{\text{H}_2\text{O}_p}$, as noted before, depend practically, so far as we know, upon capillary hydrostatic pressure and osmotic pressure. Likewise, as to $A_{\text{H}_2\text{O}_i}$, variations depend upon changes in interstitial hydrostatic and osmotic pressures. Since only colloids among the solutes present permeate capillary walls with difficulty, it is the colloid osmotic pressure differences and the hydrostatic pressure differences between capillary and interstitial fluid spaces that must be considered. An exception to this occurs during transient states while crystalloids may be coming into concentration equilibrium between plasma and tissue fluid.

Variations in P , the permittivity factor, are more difficult to treat because less is known about it. However, it is probable that in capillary endothelium there are submicroscopic "holes" and that the membrane does behave as a porous one rather than as a continuous phase layer boundary. The reasons for believing this are several, but, in the case of the lung capillaries, the little known work of Zimberg¹ provides very suggestive evidence. He showed in mammalian lungs, whose vessels were perfused with Ringer's fluid (without any colloid), that the addition of small amounts of either blood platelet suspension or India ink would greatly slow the rate of edema production. The most straightforward interpretation of his observations requires that a porous membrane be present and that the particulate matter, either platelets or India ink particles, be able to close some of the pores in order to make them unavailable to water movement. There is, according to Davson,² strong evidence for the presence of a cement substance in endothelia which normally blocks most pores to the passage of macromolecules. Wasserman and associates³ found that dextrans of molecular weight 10,000 appear in lymph at the same concentration as in plasma.

As larger molecules are studied, a sharp fall in lymph/plasma ratio occurs with molecules of 35,000 molecular weight. However, even with the largest molecules studied, in the 400,000 molecular weight range, some appear in the lymph, indicating that a small fraction of the surface of the capillary endothelium has the properties of large holes free from structural

impediments to the movement of large molecules. Danielli⁴ found that the protamine elupine increased the permeability of capillaries. Peptone was found by Shleser and Freed⁵ to have a marked local augmentation effect upon the escape of trypan blue from skin capillaries, an effect which was counteracted by adrenal cortical extracts. The specific adrenal steroid involved in the effect was not identified, although several were excluded. Davson² interprets these and other findings to indicate that the integrity of the cement substance joining cells together is a major factor in the determination of the permittivity of capillary epithelia to macromolecules. He considers that the action of narcotics and some other chemical agents may be accounted for in this way.

The problem is set in this basic framework of physical and physicochemical principles to make it clear that the somewhat complex observations to be reviewed do not violate in any demonstrable way the main earlier conclusions as to mechanisms of edemogenesis. It will, hopefully, become apparent that, in examining the newer data, one will be able to understand the processes involved more adequately by consideration of the chemical and physical mechanisms by which they are able to be brought about.

ELECTROCHEMICAL FACTORS

The reason for my own renewed interest in the lung edema problem lies in some observations on the effects of electropositive colloids and of particulate matter upon the pulmonary circulation and upon edemogenesis in the lung. It has long been known⁶ that certain dyes cause pulmonary edema upon intravenous injection. With Absolon and associates,⁷ I have reinvestigated the actions of 36 acid and basic dyes upon the dog lung, both in isolated preparations and with the lungs in an intact circulation. We have found that only basic dyes are able to cause pulmonary edema; the list of electropositive dyes having this action in our hands includes the thiazine dyes, methylene blue, toluidine blue, and toluidine blue O; the diazine dye, janus green; the triphenylmethane dye, crystal violet; and the oxazine dye, brilliant cresyl blue. Among other basic dyes, the azine neutral red; the azo dye, chrysoidin; and the pyronine dye, acridine red, did not cause lung edema. It has to be noted that as yet the chemical properties distinguishing the basic dyestuff molecules which do from those which do not produce this effect are unknown. Their dissociation constants, as given for some of them by Woislowski,⁸ do not provide a regular separation. It is possible that an exami-

nation of thermodynamic aspects of their reactions with oppositely charged particles or macromolecules might provide clues. None of 18 negative dyes tested, distributed among many organic structural groups, had any edemogenic effects. Quite obviously, a regularity has appeared. The electropositive character of the dyestuff molecule is critical to pulmonary edemogenesis.

The mechanism of this action of electropositive dye particles appears to be of interest. The erythrocyte, as is well known, bears a net negative charge. Its isoelectric point, according to Abramson and associates⁹ is below pH 3. The origin of the charge is presumably a fixed membrane constituent of acid character.

Electropositive colloids of various types might be expected to be capable of neutralizing the negative charge on red cells, thus causing them to tend to agglutinate by removing the repulsive effect of like charges. It has, in fact, been observed that electropositive molecules do have such an action. Katchalsky and associates¹⁰ have shown that polybasic amines cause agglutination of both intact erythrocytes and red cell ghosts. Polyacidic substances reverse the process, but washing with physiologic salt solutions does not.

PROTAMINES

We have observed similarly that protamines and the polybasic compound Polybrene (hexadimethrine bromide) caused red cell agglomeration. Direct microscopic studies of the effect of such substances on blood flow through the isolated dog lung have shown conclusively that plugs of agglomerated erythrocytes obstruct the pulmonary arterioles, leaving capillaries, venules, and veins narrow and with flow either slowed or stopped. Thus, there is visual evidence of what may be called agglomerated red cell embolization in large portions of the pulmonary bed following the administration of doses of 100 mg. protamine to a dog lung being perfused with 200 to 400 cc. of blood per minute (2 cc. per gm. lung per minute). Such doses raise pulmonary perfusion pressures at constant flow rates from normal values of 8 to 16 mm. Hg mean pulmonary artery pressure to values ranging from 20 to 70 mm. Hg. Smaller doses have lesser but significant effects. Levels of protamine of 20 mg. or more per 100 cc. of blood regularly induce acute massive pulmonary edema in blood perfused lungs (constant flow rate). Protamine has no such effect on lungs similarly perfused with low molecular weight dextran solutions (10 per cent Macrodex in normal saline). Lungs perfused with dextran have been challenged with protamine with negative results, and then a vol-

nine of whole blood equal to the circulating volume of dextran solution has been added. Immediately, a pulmonary artery pressure rise occurs, and the weight of the lung begins to increase.

These experiments are performed with a continuous weighing technic as described by Stish and associates.¹¹ Similar results occur if washed red cells are added to dextran perfusion fluids. When heparinized plasma or serum are employed as perfusion fluids, the results are more complex. Addition of electropositive colloids in those cases produces a transient pulmonary pressure rise and usually, but not always, a significant weight increase, sometimes out of proportion to the blood pressure rise. However, upon addition of erythrocytes, there is always a large pulmonary artery pressure elevation and massive edema ensues.

It seems that electropositive colloids could induce coprecipitation of some plasma proteins. Fibrinogen, globulins, and albumin are all on the alkaline side of their isoelectric points at normal blood pH values, consequently colloidal coprecipitation could occur under the circumstances prevailing. However, direct evidence is lacking. The indirect evidence is that the resistance to flow through the pulmonary vascular bed is increased, but it would be improper to come to any final conclusion on the basis of this finding. It is also possible that, in the presence of plasma or serum, protamines or other polybasic colloids cause the liberation of substances that affect the bore of the blood vessels, even though such polybasic colloids do not have such an effect in dextran perfused lungs.

EFFECT OF EMBOLIZATION

Since the dramatic effects of electropositive colloids and dyestuffs are seen when red blood cells are present and erythrocyte agglomeration occurs, as observed by direct microscopic observation, it seemed pertinent to study the effect of embolization of pulmonary blood vessels with chemically inert materials. The availability of glass microspheres of diameter 5 to 50 μ made such an approach possible. When such spheres are added in sufficient number to dextran perfusion fluids, the pulmonary artery pressure at constant flow rates rises sharply, and massive acute edema occurs. Approximately 10^9 microspheres of 25 μ average diameter were required to induce edema in the lungs of a 10-kg. dog. The large increase in resistance to flow induced by such massive arteriolar embolization raised the pressure necessary to maintain constant flow through the remaining patent channels. The

increased velocity of flow through those open channels requires an elevated pressure gradient for its maintenance. This is true for the segment, capillary to vein, as well as for the segment, artery to capillary. Thus, obliterating a large portion of the arborization of the circulatory bed, while total flow is maintained constant, must of necessity raise the mean capillary pressure in those portions of the arborization which remain patent. When the mean capillary pressure in patent vessels exceeds the colloid osmotic pressure, edema ensues. Following glass microsphere embolization, lungs have been seen to double their weight in fifteen minutes.

It is suggested that a similar mechanism accounts for the acute massive pulmonary edema induced by electronegative colloids and dyes in the presence of erythrocytes. These agents, by agglomerating red cells, induce arteriolar embolization. As a result, with a maintained pulmonary blood flow, the capillary pressure in patent vessels rises and the colloid osmotic pressure is exceeded, creating a situation in which in those vessels $A_{H_2O_p} \gg A_{H_2O_i}$.

PERMITTIVITY FACTOR

In the absence of erythrocytes, the action of electropositive materials upon the lung vessels is perhaps related to a change in the permittivity factor. If Danielli is correct in his inference that protamines increase the rate of edemogenesis by enlarging effective membrane pore areas, then it will be necessary to take this factor into account, not only as a major one in the absence of erythrocytes but also as a concurrent one even in their presence. Our studies on this phenomenon are incomplete, but one additional observation should be mentioned. The rate of increase in lung weight after administration of electropositive materials to plasma perfused lungs is very low at first but after ten or twenty minutes becomes progressively larger, without pulmonary pressure change, suggesting that some intermediate process with a relatively slow time constant is occurring which alters the permittivity. This might be a chemical reaction of the sort suggested by Davson,² removing intercellular cement substance and thus increasing the pore area.

It should be made clear that the emphasis put in this paper upon the role of electrochemical factors in pulmonary edemogenesis under special circumstances is not meant to suggest that such electrochemical factors are operative in many clinically significant lung edema situations. There is, for example, no reason to believe that the pulmonary edema of congestive heart fail-

ure, of increased intracranial pressure, of epinephrine overdosage, of airway resistance, or of numerous other causes is related to this phenomenon. There is ample evidence that pulmonary vascular pressure alterations can account for the above enumerated types of lung edema. However, in those pathologic states in which abnormalities of electrochemical colloid states may occur or particularly when electropositive colloidal agents are used parenterally by the physician or surgeon for any reason, as in the neutralization of heparin, it is certain that the phenomena described should be taken into account. It should be noted in addition that the lethal doses of protamine have been found to be much less in animals in shock states than those which are normal. This point may be particularly significant in relation to the use of such agents after vascular surgery.

SUMMARY

In summary, it can be said that the acute massive pulmonary edema following intravenous injection of electropositive dyestuffs and colloids appears to depend upon erythrocyte agglomeration and arteriolar embolization. The edema can be accounted for readily by the elevation in pressure in the patent capillaries that must follow such embolization of large fractions of the pulmonary vascular arborization. In addition, it seems likely that the permittivity to colloids and to water of the pulmonary capillary endothelium may be increased by additions of such substances as the protamines. These observations may be of some practical importance, perhaps, since these substances are now being employed clinically.

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This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.

THE MOST common cause of poor control of diabetes mellitus is failure to adhere to diet, often resulting from inadequate instruction. Also associated with poor regulation are social or environmental difficulties, emotional disturbances, and refusal of the patient to attempt to regulate diabetes. Some patients are resistant to diet instructions, perhaps because of emotional disturbances which encourage an appetite exceeding metabolic requirements.

Diabetic control was unsatisfactory in 126 of 160 patients with diabetes treated by insulin; of these, 83 did not have sufficient knowledge of the diabetic regime and diet. About two years later, after instruction and treatment had been given, control was good in 85, fair in 18, and poor in 57.

D. B. STONE: A study of incidence and causes of poor control in patients with diabetes mellitus. *Am. J. M. Sc.* 241:436-442, 1961.

Ruptured Mitral Chordae Tendineae in Subacute Bacterial Endocarditis

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GEORGE FAHR, professor emeritus of medicine of the University of Minnesota, who is being honored by this *Festschrift* on the occasion of his 80th birthday, is an example to his students of the consummate physical diagnostician. He delights in the opportunities presented at the bedside to translate physical findings, particularly auscultatory findings, into a rational diagnosis of the problem before him. Presented herein is a problem to please George Fahr.

Ruptured chordae tendineae of the mitral valve have been reported most commonly during or following subacute bacterial endocarditis.¹ Bailey and Hickam² found 4 such instances among cases of subacute bacterial endocarditis in 2,400 autopsies. Of 442 cases of subacute bacterial endocarditis, Cates and Christie³ found 4 ruptured chordae, an incidence of 0.9 per cent. Of 20 cases of ruptured chordae reported from the Mayo Clinic, 10 followed subacute bacterial endocarditis.¹ The chordae serve as stays to a sail withholding the leaflets of the mitral valve against the pressure of the ventricle during systole. When the stays give way, the leaflets balloon into the atria and mitral insufficiency results.⁴

The following case represents a typical example of this complication of subacute bacterial endocarditis.

CASE REPORT

C. F., a 77-year-old woman, was admitted to Mt. Sinai Hospital, Minneapolis, April 24, 1961. She dated her illness from December 1960, when she began to feel tired and weak; these symptoms gradually increased. She was twice hospitalized elsewhere and found to have an apical systolic murmur.

Five years before this admission, an apical systolic murmur of moderate intensity, presumably due to mitral insufficiency, had been found by this examiner. There was no history of rheumatic fever. In April 1961, she noted a rash on her ankles with some pedal edema.

The temperature on admission was 100° F. Blood pressure was 126/80 mm. Hg. The heart was not enlarged. At the apex, there was a grade IV systolic mur-

mur, low in pitch, with a bizarre rasping quality, accompanied by an obvious thrill. The murmur was well heard also along the left border of the heart. The apical phonocardiogram is illustrated in figure 1. The lungs were clear. The liver and spleen could not be felt. Pelvic examination was nonrevealing. A rash of petechiae was present over the ankles and feet.

The positive laboratory studies included hemoglobin of 9.5 gm. per cent; white blood count, 5,850 per cubic millimeter, with 81 per cent neutrophils; sedimentation rate, 94 mm. per hour. Urinalysis showed a trace of albumin and occasional red cells. Several blood cultures grew out *Streptococcus viridans*. Clinical diagnoses were mitral insufficiency, subacute bacterial endocarditis, and probable rupture of the chordae tendineae to the mitral valve.

She was treated daily for two weeks with 2,000,000 units of penicillin intramuscularly and 2,000,000 units intravenously and 1 gm. of streptomycin intramuscularly. For the following two weeks, the intravenous penicillin was increased to 20,000,000 units, and 1 gm. of Chloromycetin was substituted for the streptomycin. The fever did not subside until the medications were changed at the end of two weeks. She was then afebrile for two weeks, and several blood cultures were sterile in that period. Electrocardiograms showed only nonspecific T wave changes. Chest x-ray studies showed no cardiac enlargement.

She was discharged May 22, 1961, continuing penicillin therapy of 2,000,000 units orally. Two days later, her fever of 100° F. recurred. On May 26, 1961, she complained of headache. She rapidly lapsed into coma, was readmitted to the hospital, and expired the following day.

At autopsy, the heart weighed 330 gm. The mitral valve showed roughening of the edges of both leaflets, with a raised area on the free border of the mural cusp. Two ruptured chordae were identified on this cusp and on the lateral papillary muscle below (figure 2). Vegetations were visible on both cusps and attached chordae. The leaflets were moderately thickened but not stenotic, and the chief insufficiency was in the area of the mural cusp, displaced somewhat into the atrium. There were no other significant valvular or myocardial findings. There was some atherosclerosis of the coronary arteries. The spleen weighed 170 gm. An old infarct was found in the right kidney. Over the brain was a massive subarachnoid hemorrhage, with blood clot within the white matter of the left anterior hemisphere and blood in all ventricles. No mycotic aneurysm could be found, and the source of the hemorrhage could not be identified.

The microscopic sections of the mitral valve showed vegetations composed of fibrin and platelets, with areas of acute inflammatory infiltrate. No bacteria were identified in the vegetations. There were areas of destruction

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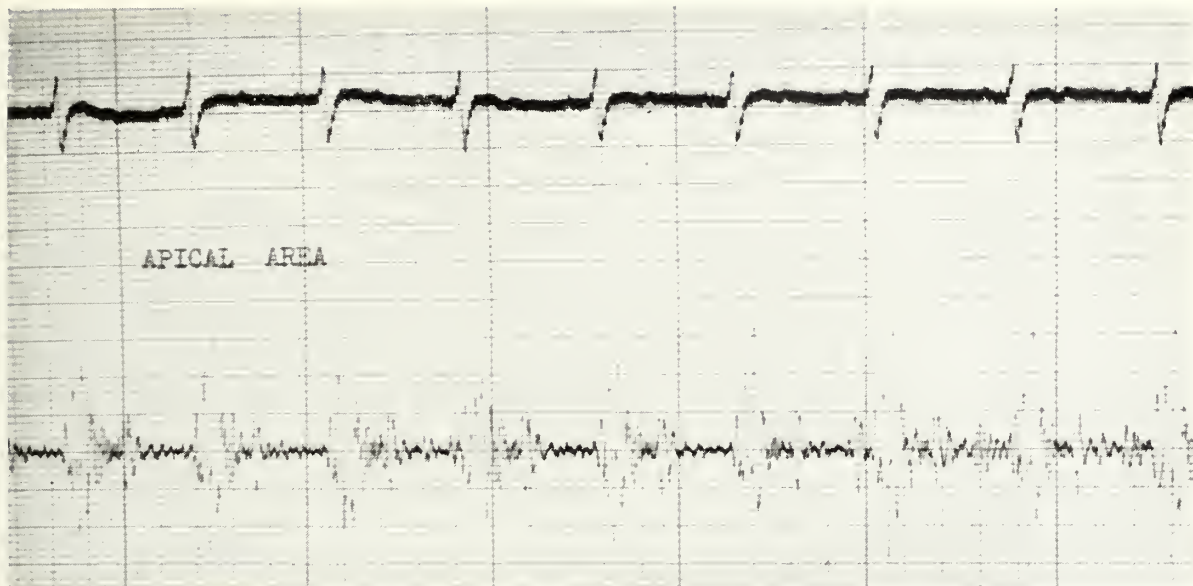


Fig. 1. Apical phonocardiogram showing great amplitude and variability of the systolic murmur

and necrosis of the valve substance with associated acute inflammation. Portions of the vegetation itself also appeared to be necrotic. There were areas of organization and fibrous tissue proliferation at the periphery of the vegetation. There was no active inflammation within the chordae. The ends of the ruptured chordae were rounded and smooth and appeared to be at least partially covered by endothelium. The papillary muscles underlying the chordae showed scattered interstitial inflammatory cells.

DISCUSSION

In this case, a previously damaged mitral valve was the seat of subacute bacterial endocarditis. Extension of the vegetations to the chordae tendineae led to rupture of several of them and to increase of the mitral insufficiency. Death caused by cerebral hemorrhage occurred five months after the probable onset of the endocarditis and one month after the diagnosis of ruptured chordae tendineae. Ruptured chordae have also been reported in the absence of bacterial endocarditis.^{1,2} Heart failure may or may not follow the separation of the chordae, which results in mitral insufficiency. In the 2 cases reported by Edwards,⁵ severe heart failure was present. Kerr⁶ states that the cardiac function may be surprisingly well maintained. Which leaflet is involved may play an important role because of the disparity in size. When the smaller mural cusp is affected, as in the case reported here, a tolerable insufficiency may result with little or no evidence of heart failure.

In the differential diagnosis, other causes of an apical systolic murmur to be considered include rupture of a papillary muscle, perforation



Fig. 2. Section through mural cusp and a chorda tendinea of the mitral valve. ($\times 10.7$) (A) Thickened free margin of valve. (B) Ruptured chorda. Note bulbous free end. (C) Area of vegetation

of the ventricular septum, ruptured mitral cusp, rheumatic mitral insufficiency, and mitral insufficiency due to a thrombus or tumor and interfering with closure of the valve.⁷ Rupture of the papillary muscle is not apt to cause a thrill.^{8,9} This lesion and rupture of the septum usually occur in a different clinical setting; that is, as a complication of myocardial infarction. Other lesions to be considered during or after subacute bacterial endocarditis are erosion of the valvular tissue and fusion of the posterior cusp to the left ventricular wall.⁵ Tumor or thrombus may interfere with closure of the mitral valve. Ruptured chordae should be considered when a systolic apical murmur appears de novo or when, as in this case, a previous systolic apical murmur increases its intensity and changes its quality. Perforation of the mitral valve cusp may also occur as a result of subacute bacterial endocarditis, producing increasing mitral insufficiency and change in systolic murmur. A possible differential point is the bizarre quality of the murmur in ruptured chordae. The systolic murmur and thrill of ruptured chordae may be present over the base of the heart and lead to the mistaken impression of aortic stenosis.¹ Perforation of the interventricular septum may also occur as a complication of subacute bacterial endocarditis.¹⁰

Pathologically, ruptured chordae must be differentiated from postmortem tears. The ends of the chordae ruptured in life are characteristically bulbous in form and may be calcified.⁵ The resulting mitral insufficiency may lead to an area of fibrosis—a “jet” lesion—on the wall of the left atrium.⁴

McGoon¹¹ in 2 cases, plicated the flailing portion of the valve, which was followed by immediate improvement which persisted during the

eight months the patients were followed. In 1 case, the preoperative peak left atrial pressure of 45 to 50 mm. Hg dropped to 16 mm. Hg after the repair. Ivalon patching of the chordae and shortening of the annulus has been reported¹² as well as Ivalon prostheses for the valve itself.¹³

SUMMARY

A case of ruptured chordae tendineae of the mitral valve occurring during subacute bacterial endocarditis is presented. This complication should be considered in endocarditis when an apical systolic murmur appears or changes its intensity or quality.

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This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.



THE PROVOCATIVE SERUM enzyme test using pancreozymin and secretin, the starch tolerance test, and the radioiodine-labeled triolein stool excretion test are recommended for detection of chronic relapsing pancreatitis. If the diagnosis is equivocal after the 3 tests, the pancreozymin-secretin test should be repeated with examination of duodenal contents. The battery of tests can be performed by a technician, except for skin-testing and intravenous injection of the hormones.

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Clinical Value of Left Axis Deviation in the Electrocardiogram: A Renaissance

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IN a *Festschrift* in honor of Dr. George E. Fahr, I have thought it possible to highlight his important early contributions to clinical electrocardiography by a discussion of the current attention to the mean electric axis of the heart, manifest in the frontal plane, and, in particular, to left axis deviation. I would venture the opinion that, had not George Fahr had such a wide interest in cardiology and the teaching thereof, he might well have had time to enunciate, in years past, many of the recent contributions elucidating the mechanisms of aberrations of the mean QRS and T axes and their clinical significance.

The article outlining the mathematical determination of the mean electric axis, written in 1913, of which he was an author together with Einthoven and de Waart,¹ will remain an electrocardiographic classic. (Waller² had developed the axis concept independently. Of interest is his discussion relating to different breeds of dogs, Waller's bulldogs having the QRS axis more to the left than did Einthoven's "long dogs.") Not as well known perhaps is the communication in 1920 by Fahr³ in which left axis deviation is related to left ventricular structure and the correct designations of right and left bundle-branch block are hypothesized. Acceptance of Fahr's deductions was much delayed, particularly as the advent of precordial electrocardiography focused attention upon chest leads as the prime indicators of right and left ventricular hypertrophy and bundle-branch block. Only in the last decade or so has the diagnostic value of the frontal vectorial loop of the QRS been widely recognized.

The varieties of cardiac disease wherein left axis deviation may be an important finding are numerous (see table). Proper attention should be accorded all features of the electrocardiogram, for instance, type of axis deviation, wheth-

er simple or complex (one might say whether the frontal-plane loop is a simple narrow ellipse or a wide complex form), the duration of the QRS, the presence and duration of the initial Q wave, and the nature of the T vector. For the "complete" electrocardiographic theoretician or diagnostician, it is an unnatural dichotomy to discuss axis deviation isolated from the total information that an electrocardiogram may convey, yet, for the sake of emphasis, that is what this communication purports to do.

CONGENITAL CARDIAC DEFECTS

The unique values of the electrocardiogram in the diagnosis of anatomic and hemodynamic abnormalities in congenital cardiac defects have been fully applied only in recent years. Witness to this claim is the precocious trend for left axis deviation in infants with ventricular septal defect or patent ductus to be related to left ven-

CARDIAC ABNORMALITIES IN WHICH LEFT AXIS DEVIATION MAY BE AN IMPORTANT FINDING

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- | | |
|---|--|
| A. Congenital cardiac defects | |
| 1. Precocious change in infancy | |
| a. Ventricular septal defect | |
| b. Patent ductus arteriosus | |
| 2. Uniquely characteristic | |
| a. Tricuspid atresia | |
| b. Atrial septal defect—"ostium primum" type of common atrioventricular canal | |
| 3. Commonly concomitant | |
| a. Endocardial sclerosis | |
| b. Anomalous coronary artery | |
| B. Acquired heart disease | |
| 1. Myocardiopathy—varied forms | |
| 2. Hypertensive heart disease <i>with</i> myocardial damage | |
| 3. Coronary sclerosis | |
| a. Myocardial ischemia with or without scarring | |
| b. Myocardial infarction—postinfarction (peri-infarction) block | |
| c. Left bundle-branch block | |
| 4. Aortic stenosis (rarely, with associated conduction defects) | |
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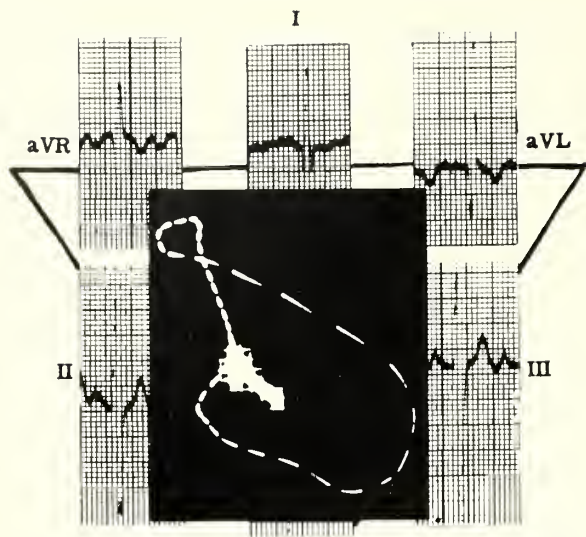


Fig. 1. Standard leads and aVR and aVL from a girl aged 5 years with ventricular septal defect. Large left-to-right shunt was present. Pulmonary pressure two-thirds of systemic pressure. Moderate left axis deviation is to be noted, with biphasic complexes and vectorial forces fitting biventricular enlargement.

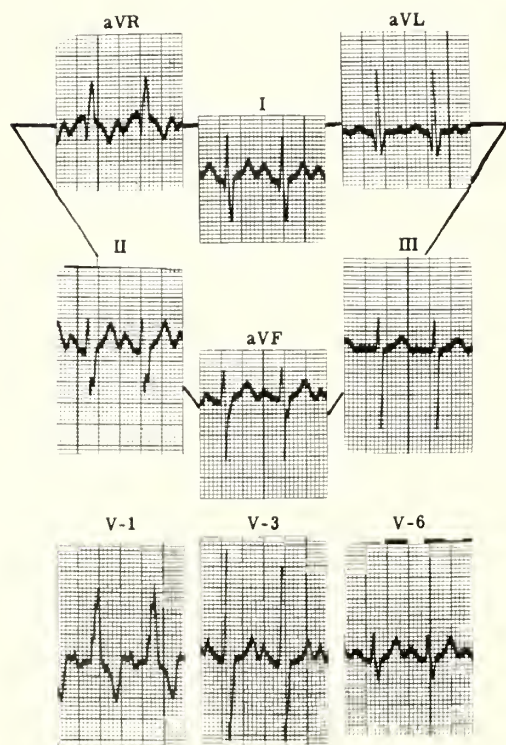


Fig. 2. Characteristic electrocardiogram of a child aged 9 years with tricuspid atresia and pulmonary stenosis. Precordial leads would support "right" ventricular hypertrophy, but rotation of QRS vectors anticlockwise in frontal plane as revealed by vectorial analysis would suggest "left" ventricular hypertrophy.

tricular enlargement, or overload (figure 1). DuShane and associates⁴ at the Mayo Clinic have included as 2 of the definite criteria for left ventricular overwork in infants less than 3 years of age an axis of the mean QRS vectors in the frontal plane of $+60^\circ$ or less and counterclockwise rotation of the QRS loop in the frontal plane. While not a universal accompaniment of tricuspid atresia, left axis deviation, with the picture of "left" ventricular hypertrophy in the precordial leads (figure 2), is sufficiently characteristic to be oftentimes the main clue to the proper diagnosis.

In the large majority of patients with atrial septal defect of the ostium primum type or of the complete form of common atrioventricular canal, the electrocardiogram shows a fairly uniform picture of left axis deviation and, thus, a most dependable indication of the nature of the cardiac defect (figure 3). Evidence that the electrocardiographic abnormality is related to a con-

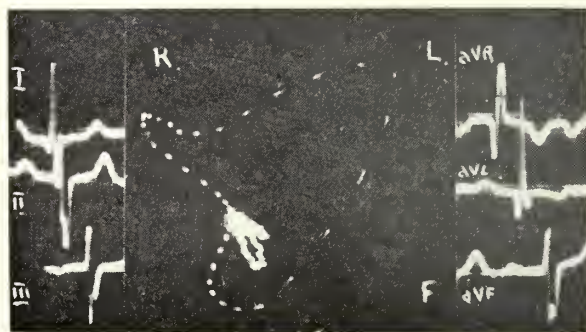


Fig. 3. Characteristic frontal vectorcardiogram of a patient with atrial septal defect of "ostium primum" variety. Patient was a girl 15 years old with a large left-to-right transatrial shunt and mitral insufficiency, grade 2 (on a basis of 1 to 4). Surgical repair was successful.

genitally defective left bundle-branch system has been presented.⁵

There is a group of patients with posteriorly located ventricular septal defects which have been called defects of the common atrioventricular canal type. Electrocardiograms of such patients usually show marked left axis deviation akin to those of patients⁶ with more definite anomalies originating from defective development of the atrioventricular cushions. Patients with the more common, anterior type of ventricular septal defect have a marked variation in the mean frontal QRS axis.⁷

A further group of patients⁸ who may characteristically have left axis deviation, particularly when pulmonary stenosis is absent, are those in whom both great vessels arise from the right ventricle and in whom there is necessarily an

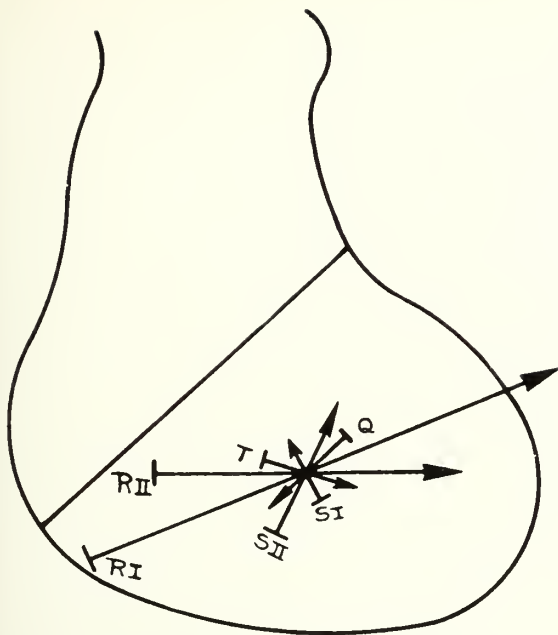


Fig. 4. Reproduction from Fahr³ illustrating his conception of manifest electromotive forces in left ventricular enlargement. Sequence of proposed vectors are Q, RII, RI (about 0.01 second after RII), SII (0.02 second later), and SI (a further 0.01 second later). Anticlockwise loop formed by heads of arrows should be of current interest.

associated ventricular septal defect. The left axis deviation will be accentuated if, in addition, left ventricular outflow is obstructed, for example, by a tiny septal defect or subaortic stenosis.

In the condition called "corrected transposition of the great vessels," there is an inversion of ventricular morphology, not uncommonly incompetence of the left atrioventricular valve, and atrioventricular conduction defects. Excitation of the left ventricle is assumedly anomalous, with the very characteristic, but not uniform, absence of a Q wave in the left precordial leads. In these cases, there is marked variation of the mean electric axis which does not correlate well with the degree of incompetence of the left atrioventricular valve. In a significant number of cases, however, there is the appearance of left axis deviation.⁹

ACQUIRED HEART DISEASE

Of widespread current interest are vectorial analyses of the sequential QRS vectors and the common usage of the terms "late left axis deviation" or "the last 0.04 second vector." I would submit that Fahr would have been completely at home in the arena of such discussion; this assertion may be supported by an illustration reproduced from his article published in 1920³ (figure 4).

Once attention has been attracted to left axis deviation, particularly that form categorized by $S_2 > R_2$ and absence of S_1 , it will be noted frequently. Many tracings will have additional abnormalities, such as negative T_1 or abnormalities in QRS or T in the precordial leads, but, in other tracings, associated abnormalities will be minimal or absent. The majority of patients will have overt coronary arterial or hypertensive disease, but a small minority will have no readily assigned cause for the electrographic aberration. The frequent association with hypertrophy is established, but it is proper to suspect left ventricular scarring (figure 5).

While this electrocardiographic abnormality of marked counterclockwise rotation of the late QRS vectors (as projected in the frontal plane) to the left (sometimes called the " $R_1S_2S_3$ pattern") is usually stable over months or years, and thus attributable to a focal organic break in the ramifications of the left bundle branch, it is not always so. A typical exception (and an indication of a functional block) is the not rare transient occur-

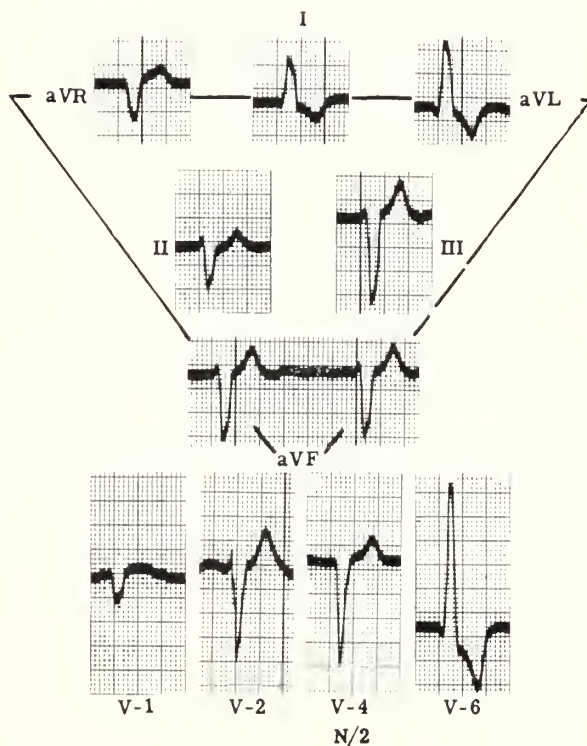


Fig. 5. Electrocardiogram from a man 77 years old who died in congestive heart failure. He had moderate calcareous aortic stenosis and a history of hypertension. Heart weighed 595 gm. Slight endocardial sclerosis was present on left side of septum. Coronary arteries showed mild luminal narrowing. There was no macroscopic or microscopic infarction or scarring of myocardium or amyloid deposition.

rence of the pattern in the electrocardiographic records following exercise in patients with coronary disease.

Aortic stenosis has been listed in the table, but emphasis must be placed on the presumed focal injury to conducting pathways of excitation. Patients who have acquired pure aortic stenosis with a thick but undilated left ventricle, so-called concentric hypertrophy, having characteristically an axis deviation in the $+60^\circ$ zone and a T vector in the diametrically opposite sextant, present the picture of a very simple frontal vectorial loop, with each standard lead showing an R and an inverted T.

In the total appraisal of the correlations of left axis deviation, a few observations concerning conditions in which it is absent but is perhaps expected to have been present may be of interest. Such cases are those of congenital aortic stenosis, coarctation of the aorta, and acquired mitral insufficiency. In the last instance, even in the presence of gross overactivity of the left ventricle and evidence of hypertrophy of the left ventricle from the left precordial electrocardiogram, there is a trend to right axis deviation, the mean QRS axis being frequently at about $+90^\circ$. The left ventricle has been grossly hypertrophied in such patients demonstrating pure gross mitral incompetence who have come to postmortem examination.

COMMENT

In patients with acquired heart disease and left axis deviation, particularly when the differentia-

tion of left ventricular hypertrophy from partial left bundle-branch block is difficult, the vectorcardiographic studies of Burch and associates¹⁰ are informative, but noteworthy is their emphasis on the need of further correlative pathologic studies.

For the electrocardiographic neophyte, Burch and Winsor,¹¹ in their latest edition of *A Primer of Electrocardiography*, were content to sum up left axis deviation succinctly by the statement, "In general, a left axis deviation of *from -20 to -30 degrees is strongly suggestive evidence of myocardial disease and -30 degrees or less is definite evidence of myocardial disease, with few exceptions.*" It may be noted that, with increasing age, healthy persons show a statistical trend to left axis deviation, but the distribution shows little overlap of a group with heart disease and "pathologic left axis deviation."^{12,13}

The electrocardiographic picture of aberrant conduction in the left ventricle has long intrigued students of electrocardiography. Wilson and Johnston¹⁴ were undoubtedly much interested in such types of aberrant ventricular excitation, as judged by the number of illustrations (including that of a case of ostium primum defect) of left axis deviation with anticlockwise rotation of the sequential instantaneous QRS vectors in their early paper on vectorcardiography (figure 6).

The contribution of Grant¹³ to the understanding of the pathologic correlates of left axis deviation, particularly late QRS vectors in the -0° to -60° sextant, has had widespread influence.

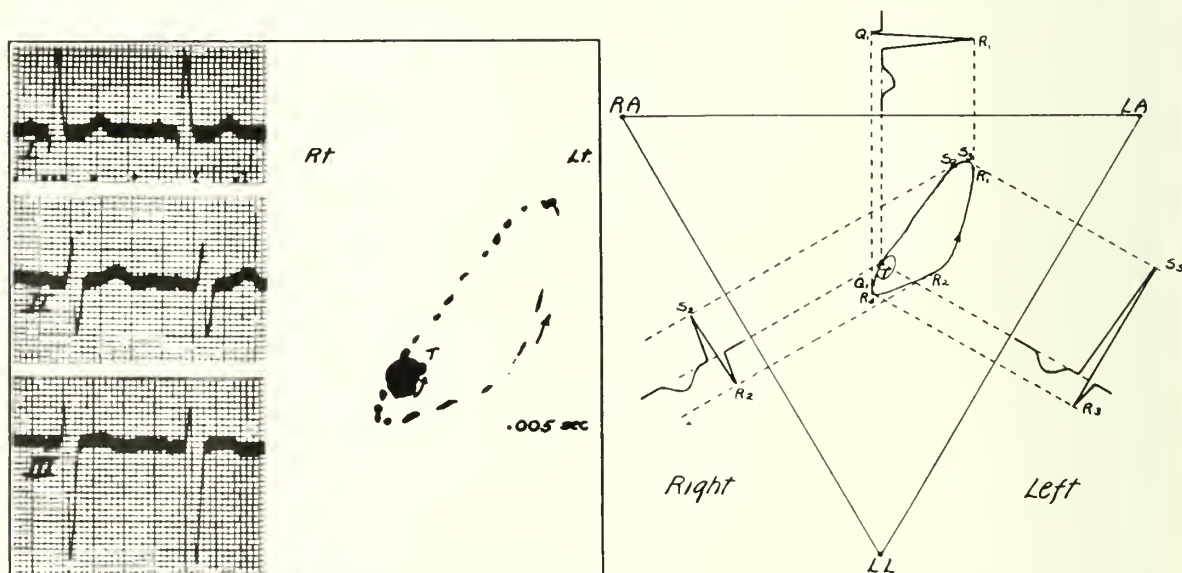


Fig. 6. Reproductions illustrating “late left axis deviation” and a conventional method interrelating frontal vectorcardiogram and standard leads. Currently, demonstration is usually based on a figure of 3 lines crossing at their centers at angles of 60° , giving the sextants (triangle is “imploded”). (From Wilson and Johnston.¹¹)

Such abnormal tracings with "late left axis deviation" may be regarded as related to either a congenital or an acquired conduction defect in the left bundle system and are frequently the consequence of gross subendocardial infarction, usually in the anterolateral wall. In the electrocardiographic abnormalities related to aberrant conduction consequent to myocardial infarction, the QRS is usually increased, but this is not necessarily so, as Grant¹⁵ and Pruitt and I¹⁶ have pointed out. Abnormal vectors may be displayed by an alteration in the sequence of excitation of the heart without the requirement of an over-all delay. Indeed, in historic perspective, one of the rather perplexing findings in the experiments of Rothberger and Winterberg¹⁷ and Wilson and Herrmann,¹⁸ as well as later of Pruitt and associates,¹⁹ was the maintenance of a normal QRS interval in the face of extensive damage to the peripheral left bundle-branch system.

Moll and von Lutterotti²⁰ and Duchosal and Jornod²¹ have also pointed out the pathologic significance of the $R_1S_2S_3$ pattern. The latter emphasized the relative frequency of this electrocardiographic aberration and that there would be a focal anatomic lesion but that in a significant number of instances the aberration apparently would not be related to acquired disease. In the electrocardiographic illustrations published by Pruitt and associates^{22,23} on lateral-wall and subendocardial infarctions, it may be observed that this pattern was not uncommonly manifest. The study of Davies and Evans²⁴ gave further support to Grant's conclusions regarding the need for a focal lesion in the production of late left axis deviation, although a few instances were encountered in which no conclusive evidence of heart disease was present. Of interest was their observation of a high incidence of this vectorial display in patients with various types of myocardiopathy other than that associated with hypertensive or coronary-artery disease. Reference should be directed also to the paper of F    r and associates,²⁵ wherein is found vectorcardiograms and electrocardiograms of patients with chronic Chagas' disease, and to the paper of Schamroth and Blumsohn,²⁶ wherein is reported a high incidence of left axis deviation in the African with heart disease, a population group practically devoid of coronary sclerosis but afflicted not infrequently with cardiomyopathies with endocardial sclerosis.

One must recognize that, as a concept of block, delayed excitation through a conducting pathway may result in the same electrocardiographic aberration as complete and irreversible

block in that pathway. Scherf²⁷ in particular has seen the need of emphasizing this fact. The reversible electrocardiographic aberrations with left axis deviation produced by Rasmussen²⁸ by distention of the left ventricle are of particular interest in this setting. While stepwise changes in left intraventricular block patterns may be observed in persons with coronary and hypertensive disease, the patient who has a $R'S''S'''$ configuration, with a slightly prolonged QRS interval, usually maintains such a pattern for long periods without change.

SUMMARY

The importance of study of standard leads and determination of mean electric axis in the frontal plane for diagnostic electrocardiography is re-emphasized. The original contributions to this field by Dr. George Fahr, octogenarian today, are acknowledged.

The contribution to electrocardiographic diagnosis realized by recognition of left axis deviation may be particularly important in both congenital and acquired heart disease. The unique features of left axis deviation, with the mean QRS axis in the 0° to 60° sextant, in practically all cases of low atrial septal defects of the ostium primum type or of complete atrioventricular canal, have diagnostic reliability far in excess of average electrocardiographic diagnoses.

Late left axis deviation related to intraventricular block, particularly when there is prominent anticlockwise rotation of the terminal QRS vectors with and without widening of the QRS, should be recognized as indicating a focal lesion in the left ventricle, usually but not necessarily related to ischemic heart disease.

The author was privileged to have been associated with Dr. Fahr in the University Hospitals outpatient heart clinics during the period that he had an assignment in the laboratory of Dr. Maurice Visscher in 1938 and feels indebted to Dr. Fahr for many practical and theoretic points that have proved important in cardiologic practice.

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This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.

FAMILIAL EMPHYSEMA appears at an earlier age than is usual with diffuse obstructive emphysema, suggesting that lung tissues of such persons may be inherently weak. Genetic factors may outweigh the influence of sex, since familial emphysema is often found in women, even though emphysema is predominantly a male disorder.

In addition to the possibility of hereditary tendencies, causative agents and multiple pathogenic pathways thought to be responsible for the development of emphysema are chronic recurrent bronchiolar infection, severe coughing, inflammatory swelling of the bronchiolar mucosa with impairment of ciliary action, premature aging, primary disorders of the pulmonary or bronchial circulation, and structural defects of the thorax. Weakness of the tissues distal to the terminal bronchioles appears to be important in the pathogenesis. Pulmonary emphysema may be classified as (1) obstructive or diffuse, including lobar, unilateral, and bilateral, and (2) bullous, including isolated or unilocular and multicentric.

In 2 families, 9 members were affected by progressive pulmonary insufficiency caused by emphysema. Several other family members had bronchopulmonary disturbances.

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The Problem of Immunological Deficiency

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DURING THE LAST FEW YEARS, intensive research efforts in a number of laboratories have focused on the immunologic deficiency diseases and their implications for a host of unresolved basic and clinical problems. Two of these diseases, agammaglobulinemia-hypogammaglobulinemia and Hodgkin's disease, have been central to our research program in immunology, and data from these studies will be the basis of most of the discussion to follow. A third disease, sarcoidosis, may also be classified as an immunologic deficiency disease and will be mentioned briefly, with indications of some of its implications.

AGAMMAGLOBULINEMIA-HYPOGAMMAGLOBULINEMIA

Although the link of the gamma globulins to antibody production was established by Tiselius and Kabat¹ in 1939, the earliest recognition of the relationship of gamma globulin deficiency to inordinate susceptibility to bacterial infection was that of Colonel Ogden Bruton in 1952.² This was a remarkable clinical insight, a point missed by other well-informed, well-equipped observers, and it served as a point of departure for a wide range of research efforts. In less than ten years, it has yielded not only an astonishing amount of data but an extraordinary number of useful hypotheses regarding the role of gamma globulin and antibody production in (1) recovery from and resistance to bacterial and virus diseases; (2) the etiology of the so-called autoimmune diseases, the enigmatic mesenchymal diseases, malignancy, leukemia, and a variety of hematologic disorders; (3) hypersensitivity in its various forms; (4) the homograft reaction; and (5) many other significant problems. Unlike Hodgkin's disease or sarcoidosis, which involves relatively narrow, apparently isolated immunologic deficiency, agammaglobu-

linemia involves a broad area of inadequate function, an area still partially undifferentiated and undefined. Even now, granting all that is known and all that has been done, it presents an enormous potential for further research.

Over 300 cases of agammaglobulinemia have been reported in the literature; many of these are isolated cases, but more than half have been studied by 1 of 5 or 6 research groups.³⁻⁸

The University of Minnesota series of agammaglobulinemic patients has included 34 children with congenital disease—23 boys with the sex-linked recessive type, having gamma globulin levels below 20 mg. per cent, and 11 children, 9 boys and 2 girls, with the congenital sporadic form, having somewhat higher gamma globulin levels, 90 to 339 mg. per cent. In addition, we have studied 10 adults with primary acquired agammaglobulinemia whose gamma globulin levels range from 5 to 100 mg. per cent. All of the boys in the sex-linked recessive group and most of the adult patients lack the other immunoglobulins, β_{2A} and β_{2M} , as well; some of the children in the congenital sporadic category have one or the other but rarely both. All have almost complete lack of antibody in the serum. Barandun³ considers this lack of antibody to be the salient characteristic of the disease and refers to it as lack-of-antibody syndrome (Antikörpermangelsyndrom). The adult patients and the children with the congenital sporadic form of agammaglobulinemia have shown minimal immunologic responsiveness to some types of stimulation. The boys with the congenital sex-linked disease are almost completely inert immunologically; however, a number of them have never demonstrated detectable antibody of any kind despite intensive antigenic stimulation, although there is every reason to believe that they also retain some vestige of antibody-producing capacity.

Most agammaglobulinemic patients present with a history of frequent, severe infections with the extracellular bacterial pathogens—pneumococci, beta hemolytic streptococci, hemophilus, meningococci, and staphylococci. Usually, the

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most frequent manifestation has been pneumonia, almost equalled in frequency by conjunctivitis, sinusitis, and otitis. Meningitis, septicemia, gastrointestinal disturbances, and pyoderma have also been problems.

Most virus infections are handled well by this group of patients. The course is normal in severity and duration, and resistance is established, although there is rarely any response to repeated stimulation with virus antigens.⁹ There are, however, a few indications of increased susceptibility, such as recurrences of mumps and chickenpox;^{2,3} severe courses of poliomyelitis and chickenpox;^{3,9,10} occurrence of vaccinia gangrenosa;^{11,12} and progression of homologous serum hepatitis to chronic, fatal liver disease in every recorded case.^{3,5,9}

Our cumulative experience with the many infections of these patients has indicated a greater-than-chance occurrence of respiratory and urinary tract infections with invaders of the coliform group. The circumstances suggest that these infections may be secondary to hospitalization and antibiotic therapy for infections with the pyogenic pathogens, and the question of increased susceptibility is being kept open. Another association of interest, discussed in detail elsewhere,¹³ is the occurrence of *Pneumocystis carinii* pneumonia in agammaglobulinemic infants.

Agammaglobulinemic patients are generally maintained on periodic injections of gamma globulin and/or antibiotics, with treatment of intercurrent infections as they occur. The inadequacy of these efforts is indicated by the death of 10 of the 23 boys with the sex-linked recessive form of the disease and 2 of the 10 adults with primary acquired agammaglobulinemia.

Aside from the experience with infectious disease, study of agammaglobulinemic patients and their families has shed light on a number of unresolved disease problems. For example, these patients and their relatives have an unusually high incidence of rheumatoid arthritis, and the frequency of other mesenchymal diseases is far beyond the chance level.^{14,15} This adds weight to arguments for an inherited predisposition to diseases of this group, suggests a genetic basis for acquired agammaglobulinemia, and implies that "collagen diseases" are related in some unknown way to the abnormal reticulum presumably responsible for failure of plasma cell production and consequent immunologic inadequacy. This experience also shifts speculation regarding the pathogenesis of these diseases away

from excessive gamma globulin or antibody production, autoantibodies, and similar concepts.

Speculation has also linked chronic liver disease following acute infectious hepatitis to humoral hypersensitivity and autoantibodies. However, 2 of our agammaglobulinemic patients, and 2 others to our knowledge,^{3,5} have died of chronic liver disease following infectious hepatitis; all patients were almost completely lacking in plasma cells, gamma globulin, and circulating antibody.

As more and more patients with agammaglobulinemia are studied, it is of particular interest to note the coexistence of anomalies and diseases other than the usual infections. Some of these have already been noted. The hematologic abnormalities have been of great interest because of their implications for the nature of the basic mesenchymal defect. A considerable body of data has accumulated indicating that failure of plasma cell production is not always an isolated defect but is sometimes accompanied by relative failure of production of other cell types as well, such as lymphocytes,¹⁶ neutrophils,¹⁷ eosinophils,¹⁸ platelets, and red blood cells.¹⁹ There is also evidence that blood dyscrasias occur with considerable frequency in relatives of agammaglobulinemic patients.²⁰

About 30 per cent of leukemic patients have hypogammaglobulinemia,²¹ assumed to reflect the dominance of the leukemic process in the reticuloendothelial system and secondary inadequacy of immunologic adaptation. However, recent experience has indicated that an alternative interpretation may be warranted in some instances. A 4-year-old boy, followed in our laboratory from birth, had congenital sex-linked recessive agammaglobulinemia, as did an older brother. He had a very good clinical history, and, aside from the deficiencies of the immunoglobulins and the concomitant lack of plasma cells, blood and bone marrow findings were normal. Following an injection of tetanus antitoxin for a burn, persistent skin reactions and fever developed, which were later accompanied by respiratory difficulty. Roentgenograms showed thymic enlargement, and blood and bone marrow studies revealed acute lymphatic leukemia. The disease followed the course of fulminant acute lymphatic leukemia in childhood. Page and associates²² had a similar experience. A child, followed closely for a year and a half because of profound hypogammaglobulinemia and dermatomyositis, died of lymphatic leukemia at about 4 years of age. Several possible explanations have been suggested: agamma-

globulinemia and leukemia may have a common origin in faulty organization and function of reticular tissue; agammaglobulinemic patients may be more susceptible to the virus responsible for the leukemic process; or they may be unable to cope adequately with mutational changes in their own cells, a hypothesis relating this development to the deficient homograft reaction seen in some agammaglobulinemic children. In this connection, the incidence of malignant processes in these patients may merit reconsideration; up to this time, it has been considered random.

One type of tumor, benign thymoma,^{19, 23-27} has been associated with acquired agammaglobulinemia in a number of cases. This finding has gained additional significance in the light of recent experimental studies which seem to link the thymus to the development of immunologic capacity.^{28, 29}

Experience with skin homografts and lymph node transplants in agammaglobulinemic patients has been mixed. A skin homograft has survived intact for more than six years in one of our patients, and such grafts have survived for extended periods before ultimate rejection in other cases. Prolonged survival is not the rule by any means, however, and a number of instances of early rejection have been noted.^{30, 31} Lymph node transplants have functioned for as long as one hundred and forty days.³² Rejection is, of course, more consistent with prevailing concepts of the role of cellular immunity in the homograft reaction and more consistent with our own experience of prolonged graft survival in Hodgkin's disease patients, as discussed in the next section. Although not yet reconcilable with other data, these findings in agammaglobulinemic patients seem to warrant inclusion of deficient transplantation immunity as another facet of their disturbed immunologic function.

Various forms of skin sensitivity have been studied in this patient group, among them wheal and erythema sensitivity and delayed allergy. There is evidence from two sources that wheal and erythema sensitivity is lacking in agammaglobulinemic patients. Using the method of Kailin and associates,³³ we were unable to induce this form of sensitivity in any of 6 agammaglobulinemic children. To the contrary, using this method, we did induce wheal and erythema allergy in 8 of 9 immunologically normal children. In the agammaglobulinemic children, delayed allergy to the antigen (an *Ascaris lumbricoides* extract) developed. This reactivity was successfully transferred to normal recipients with

peripheral blood leukocytes but not with serum. The other evidence regarding lack of wheal and erythema sensitivity comes from the history of one of the adult patients. For some years, generalized urticaria and severe gastrointestinal manifestations appeared when this woman ate fish; after the onset of her agammaglobulinemia, this sensitivity disappeared.

The results of delayed allergy investigations in this group are not entirely consistent,³⁴⁻³⁸ and their interpretation is hampered by the relatively insensitive, nonquantitative methods for assessing degree of susceptibility and response. However, the weight of evidence is that delayed reactivity in agammaglobulinemic patients is generally intact and of normal vigor. It is of particular interest that delayed allergy to 2,4-dinitrofluorobenzene, diphtheria toxoid, and horse gamma globulin developed in 2 of the children who showed a deficient homograft response.

Several other aspects of cellular immunity—the inflammatory response,³⁹ surface phagocytosis,⁴⁰ and the migratory capacity of leukocytes⁴¹—have also been studied in these patients and found to be normal.

HODGKIN'S DISEASE

It has been known for many years that Hodgkin's disease patients are particularly susceptible to infections with intracellular pathogens: tuberculosis,⁴² brucellosis,⁴³ cryptococcosis,⁴⁴ and other fungus diseases⁴⁵ and that such patients seldom show a positive skin reaction to tuberculin.⁴⁶ More recently, Schier and associates^{47, 48} demonstrated that this anergy is not specific to tuberculin but extends to a number of other antigens as well. In an effort to define this apparent immunologic defect further, we studied delayed reactivity in a large group of Hodgkin's disease patients, using a battery of antigens. Of this patient group, 60 per cent showed no reaction to any antigen compared with less than 2 per cent in the control group.^{49, 50} The data confirmed that the anergy appears early in the course of this disease and is not secondary to debility, as in cancer and leukemia patients. Subsequent studies⁵¹ have shown that delayed reactivity cannot be transferred to these patients with living leukocyte suspensions from sensitive donors.

The loss of delayed reactivity in Hodgkin's disease appears to be an isolated defect. These patients are able to react to histamine and to accept passive transfer of immediate reactivity to such antigens as ragweed extract and guinea pig serum.⁴⁸ Supplementary data from our study

previously cited show that they have normal gamma globulin levels, serum agglutinins, and response to immunization procedures.

Skin homografts were attempted in a number of Hodgkin's disease patients while they were in good condition and expected to remain so for several months. Three grafts, all in patients anergic to the entire test battery, survived for extended periods, 2 for the remaining lifetime of the host. Early rejection of homografts was seen in 4 instances, including 2 patients who had mildly positive reactions to at least 1 of the skin test antigens.

SARCOIDOSIS

Sarcoidosis, a disease of unknown etiology, is also characterized by a disturbance in immunologic mechanism, a loss of delayed reactivity to a variety of antigens.⁵² The loss resembles that of the Hodgkin's disease group in that it is a relatively isolated one. The patients show un-

impaired ability to form circulating antibody,⁵³ have a normal skin response to histamine, and show the Prausnitz-Küstner reaction with ragweed.⁵⁴ Original studies indicated that sarcoidosis patients demonstrated delayed allergy following transfer of viable leukocytes from sensitive donors,⁵⁵ differentiating them from the Hodgkin's patients who do not show such conversion.⁵¹ However, Lawrence,⁵⁶ in further study of sarcoidosis patients, recently showed that there is a transfer of local reactivity only and not systemic conversion, as was originally supposed. Studies of the homograft response in this group are indicated.

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WHEN CARCINOMA completely obstructs the right colon, prognosis is poor. The lesion is rare. Spread is by embolization rather than by permeation, edema and hyperperistalsis probably promoting dissemination of cancer cells along the afferent lymphatics and blood vessels.

Completely obstructing growths are usually located near the hepatic flexure, whereas partially obstructing or nonobstructing lesions are in the cecum or the ascending colon. With complete obstruction, lesions are small and almost always annular and ulcerative.

Crampy abdominal pains, constipation alternating with diarrhea, and nausea and vomiting are prominent with complete obstruction. Gross melena occurs as often with partially obstructing and nonobstructing lesions as with completely obstructing growths. Most patients with any type of right colonic carcinoma are anemic; blood loss is comparable for small and large growths. With complete or partial obstruction, abdominal distention is frequent but a mass is rarely palpable. With nonobstructing lesions, a mass is often felt in the right lower abdominal quadrant. With complete obstruction, barium roentgenograms invariably demonstrate blockage.

During a thirty-four-year period, 20 patients with complete obstruction of the right colon by carcinoma were seen. Of the patients, 11 were women and 9 were men. All the subjects were treated by right hemicolectomy; 16 had had a preliminary decompressive procedure. Only 22 per cent of patients with lesions obstructing the hepatic flexure survived five years; both of 2 subjects with growths blocking the cecum died within three years after operation. Five-year survival rate for patients with complete obstruction of ascending colon was 33 per cent, about half that for patients with partially obstructing or nonobstructing growths.

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Effect of Fibrinolytic Agents on Experimental Myocardial Infarction

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FIBRINOLYTIC AGENTS given locally or systemically have proven effective in the dissolution of clots in arteries or veins.^{1,2} However, despite the fact that significant numbers of patients have been treated with these fibrinolytic agents, there is no definite clinical or pathological evidence of benefit from such therapy.^{3,4} The purpose of thrombolytic therapy is to dissolve blood clots, but only 60 per cent of patients who come to autopsy after acute myocardial infarction have fresh thrombi.⁵ Also, it has long been a dictum that the myocardium deprived of its arterial blood supply is not viable after thirty minutes.^{6,7} Nevertheless, under conditions of hypothermia and perfusion of the coronary blood vessels with heparin, the myocardium may recover normal function after two hours of complete stoppage of blood flow.^{8,9} Experimentally it has been demonstrated that clots of three or less days of age can usually be completely dissolved, that clots of three or four days can be partly dissolved, and that those existing for more than four days are resistant to plasmin or streptokinase infusion.¹⁰ These obvious facts seem to present formidable clinical obstacles to the treatment of patients with acute myocardial infarction.

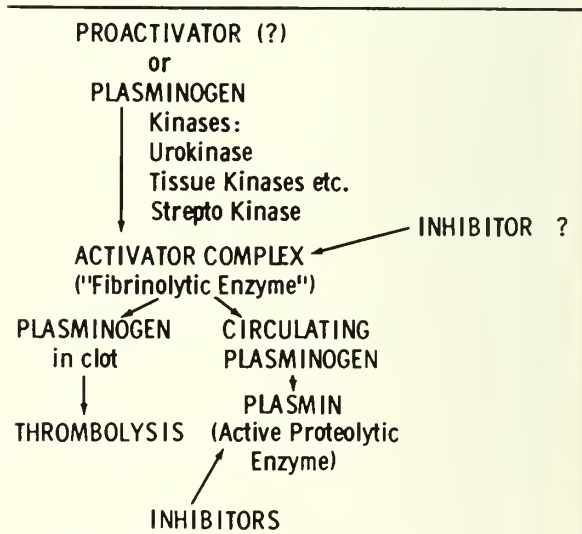
Our experiments were designed to determine if clots within the coronary vessels could be dissolved within a reasonable period by fibrinolytic therapy and whether such treatment had any influence on the evolution of acute myocardial infarction.

Many workers have studied the physiology of the fibrinolytic system. As outlined in table 1, Christensen and McLeod, Astrup, Sherry and his co-workers, and Kline and Fishman have shown that this system is dependent upon the activation of plasminogen, a circulating globulin

contained in fractions I and III of Cohn.¹¹⁻¹³ There is some evidence that there is a large amount of circulating proactivator which may be identical to plasminogen. In the presence of tissue kinase, blood kinase, or activators such as streptokinase or staphylokinase, plasminogen is converted to an activator complex which is the fibrinolytic enzyme. Thus, the enzyme precursor, plasminogen, is converted into the active proteolytic enzyme, plasmin, in the circulating blood.

In addition, the protein fraction of blood contains inhibitors which inactivate plasmin (anti-plasmin) and also contains a probable inhibitor to the activator complex. Stress situations, such as violent exercise, severe anxiety, surgery, shock, or burns may activate plasminogen, and it is well known that nicotinic acid given intravenously is followed by a definite increase in fibrinolytic activity.¹⁶ Inhibition of the system follows the ingestion of saturated but not unsaturated fats or of cholesterol; in vivo, it occurs in the presence of soy bean extracts or trypsin.¹⁷ Tissue kinase is

TABLE 1
MECHANISM OF FIBRINOLYSIS



From the Sloan-Kettering Division of Cornell University Medical College, and the Departments of Medicine and Surgery, Memorial Center for Cancer and Allied Diseases, New York City, and the Andre & Bella Meyers Laboratory of the Sloan-Kettering Institute, New York City.

known to be present in heart muscle, arteries, brain, lung, uterus, adrenals, prostate, and body fluids and probably plays a very important but as yet unassessed role. This activator is apparently absent in the liver, kidney, skeletal muscle, and spleen. The presence of plasminogen in clots may be crucial since it may trigger the process of their dissolution. This is suggested by the fact that these clots can be dissolved by giving an activator such as streptokinase in excess of circulating antistreptokinase but not by giving preformed plasmin. Excesses of activator complex, however, may deplete plasminogen levels and, in such situations, the administration of plasmin is preferable.

TABLE 2

FACTORS INFLUENCING IN VIVO THROMBOLYSIS

- 1 Enzyme / substrate ratio
- 2 Amount of Plasminogen in the Thrombus (~ circulating Plasminogen levels)
- 3 Amount of enzyme delivered to thrombus (hemodynamic factors)
- 4 Inhibition of activator complex (?)
- 5 Interference with Plasminogen activation in the clot
 - a Presence of specific inhibitors in the clot ?
 - b Interference with diffusion of activator complex into the clot

The fibrinolytic system is subject to the same general conditions that control any enzyme system (reviewed in table 2). It has also been shown that dissolution of clots is dependent upon their fibrinogen content; a clot high in fibrinogen is resistant to fibrinolysis.²⁰ Also of interest is the fact that hyperlipemia or the presence of fat in clots inhibits fibrinolysis and results in a rise in antifibrinolysin levels.^{21,22}

EXPERIMENTAL STUDIES

A segment of the anterior descending coronary artery was exposed, as shown in figure 1. Thrombi were produced by local injection of a mixture of blood and serum into an isolated coronary artery using the modified Wessler technic.²³ Visualization of the occluded segment was obtained by local injection of radiopaque material into the side branch. Arteriograms were taken before and at repeated intervals. Control animals were given an intravenous infusion of saline over a

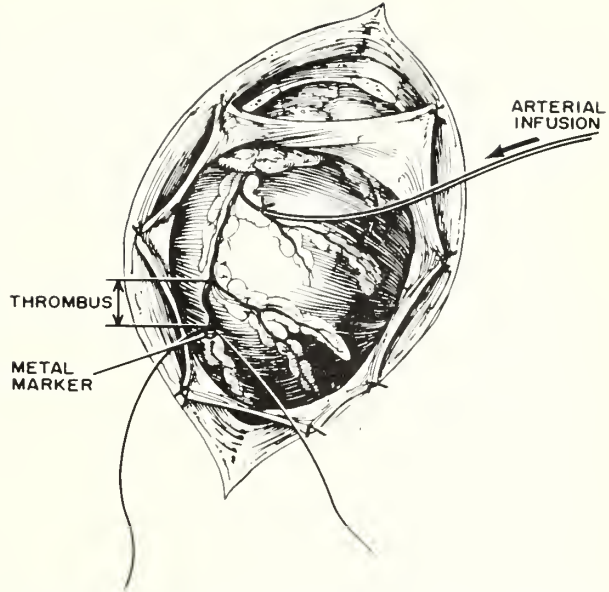


Fig. 1. Technic of producing and visualizing coronary thrombi

period of eight to twelve hours. In the treated animals, an intravenous infusion containing 40,000 units per hour of plasmin was begun one to

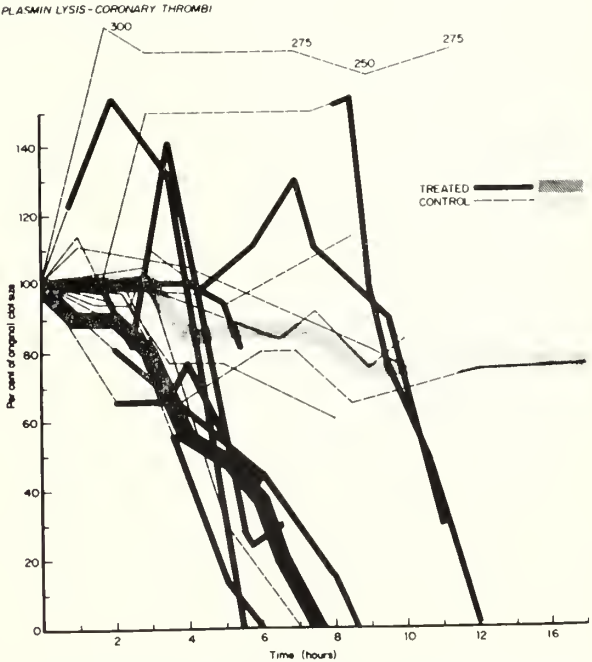


Fig. 2. Line graph indicating the change in clot size with time of the 9 animals receiving thrombolytic therapy and of 9 control dogs. The heavily stippled line represents the average change in clot size of the treated group, and the lightly stippled line the average change in clot size over the period of observation in the control animals. Individual animals in the treated group are represented by solid heavy lines and the control group by interrupted lines.

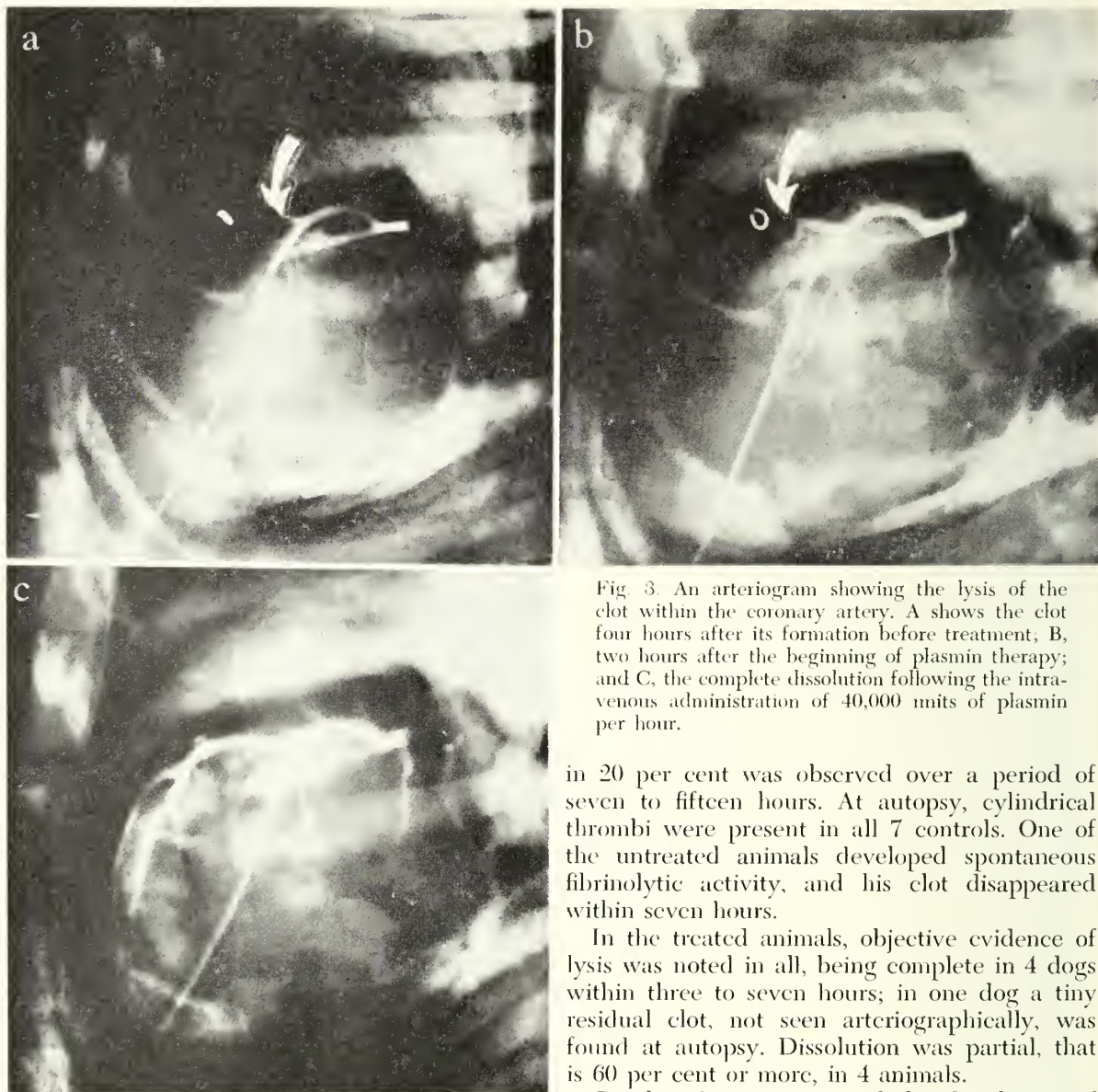


Fig. 3. An arteriogram showing the lysis of the clot within the coronary artery. A shows the clot four hours after its formation before treatment; B, two hours after the beginning of plasmin therapy; and C, the complete dissolution following the intravenous administration of 40,000 units of plasmin per hour.

in 20 per cent was observed over a period of seven to fifteen hours. At autopsy, cylindrical thrombi were present in all 7 controls. One of the untreated animals developed spontaneous fibrinolytic activity, and his clot disappeared within seven hours.

In the treated animals, objective evidence of lysis was noted in all, being complete in 4 dogs within three to seven hours; in one dog a tiny residual clot, not seen arteriographically, was found at autopsy. Dissolution was partial, that is 60 per cent or more, in 4 animals.

Graphic demonstration of the dissolution of these clots is shown in figure 3A, B, and C. In A, the clot has been present for eight hours prior to treatment; B shows beginning dissolution of the clot after two hours of plasmin therapy and C demonstrates the complete dissolution at the end of a four and one-half hour infusion of fibrinolysin.

The microscopic differences in the control and treated series were striking and are summarized in figure 4. Autopsies were done ten to fifteen hours after coronary occlusion. In the untreated dogs, microscopic evidence of marked interstitial edema, dilatation and congestion of the capillary vessels, scattered focal necrosis of muscle fibers, well-developed fibrinous epicarditis and subepicardial infiltration, and the presence of micro-

eight hours after clot formation. Such dosage resulted in increased fibrinolytic activity with euglobulin times of less than an hour. Infusion was continued until clot lysis was complete, and the animals were sacrificed an hour after disappearance of arteriographic evidence of filling defect.

Figure 2 is a graph showing the results of plasmin therapy in 9 control and 9 treated animals. The heavy line represents the per cent of the original clot size in the treated, and the dotted lines that of the original clot size in the control animals. Time is given on the abscissa and per cent of original clot size on the ordinate. In 7 control dogs observed over a period of twelve hours an average decrease, or shrinkage, of clot

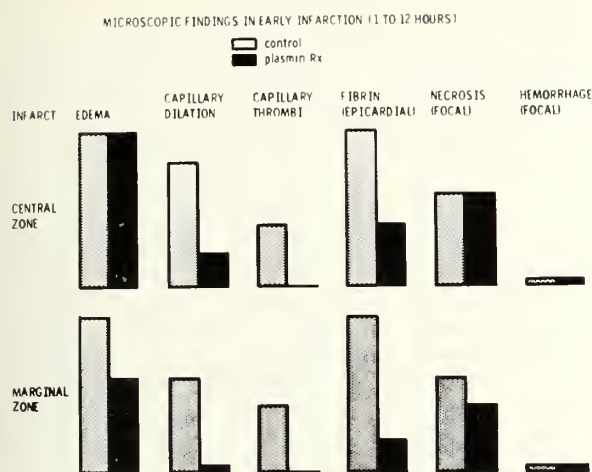


Fig. 4.

thrombi in both central and marginal areas were noted. In the dogs receiving plasmin, it is obvious that interstitial edema and capillary dilatation were much less and microthrombi were not seen in the marginal zones. There was significantly less deposition of fibrin in both central and peripheral areas. Since the microscopic differences were the same in these experiments as in the next group, they will be discussed at that time.

Sixteen control and 20 treated dogs were similarly operated upon: a removable clamp was placed so as to occlude the artery, and then the chest was closed. After three hours of occlusion, the clamp was released. The control dogs were sacrificed seven hours to two weeks later. Two hours after the beginning of occlusion, the 20 treated animals were given plasmin as previously described, and one hour later the clamp was released. Plasmin infusion was continued for four more hours, that is, for a total of five hours. All dogs were sacrificed seven hours to two weeks later, and the hearts were examined for gross and microscopic changes. Figure 5 summarizes the gross changes seen in the treated and control animals. Large confluent transmural myocardial infarction was found in 11 of the control animals and in two of the dogs with fibrinolytic activity of one to two hours. Confluent apical and/or subendocardial infarction was seen in 4 of the controls, and in 3 of the dogs with good fibrinolytic activity. Spotty focal intramural infarcts were noted in only 1 control animal, in 5 dogs with a euglobulin time of less than an hour, and in 3 dogs with a euglobulin time above one hour. Spotty subendocardial necrosis was found in 5 animals with good fibrinolytic activity, but was not present in any of the controls or in any of the inadequately treated dogs.

No evidence of infarction was present in 2 treated animals, although these died very soon after coronary occlusion.²⁴

MICROSCOPY

The animals with marked fibrinolytic activity, that is, a euglobulin lysis time of one hour or less, had 25 to 50 per cent smaller, and often spotty, infarcts with regression into the apical and subendocardial regions. Only one of the control animals had a spotty focal intramural infarction.

The microscopic changes in both series of animals were essentially the same, but the differences were quite striking, particularly in the marginal or peripheral zone of the infarct. Notable were the absence of capillary dilatation, microthrombi, and the deposition of epicardial fibrin in the treated, as compared with the control dogs. Figure 6 is a photomicrograph of a twelve-hour old untreated infarct; a section from the central zone demonstrates marked interstitial edema, shrinkage of the muscle fibers and massive platelet aggregation in the dilated vessel. A specimen of the same infarct taken from the marginal zone shows thrombi in the capillaries and venules (figure 7).

Figure 8 is a photomicrograph of a thirteen-hour-old infarct in which coronary circulation was restored after six hours of plasmin treat-

Infarction		FIBRINOLYTIC SALVAGE OF INFARCTED MUSCLE									
		(1	1	2	3	4	7	14	21	28	
Large Confluent Transmural			○	○	○	○	○				
Confluent Apical and/or Subendocardial					○		○	○		○	
Spotty Focal Intramural		●	●	●	●		○	○	○		
Spotty Subendocardial		+		+	+		Control				○
None		+					Fibrinolytic Activity				○
							> 1 H				○
							< 1 H				●
							< 1 Hour Fatal				+

Fig. 5. Describes the gross autopsy findings and indicates schematically the size of infarcts found in the various groups. The open circles represent the controls; the solid circles, the treated animals with euglobulin lysis times less than one hour; the notched circles, treated animals with euglobulin lysis times of one to two hours; and the solid circles with crosses, the treated animals which failed to survive the procedure. In the control animals, infarctions were usually large, confluent and transmural, while the treated animals tended to have small apical, intramural, subendocardial spotty infarctions.

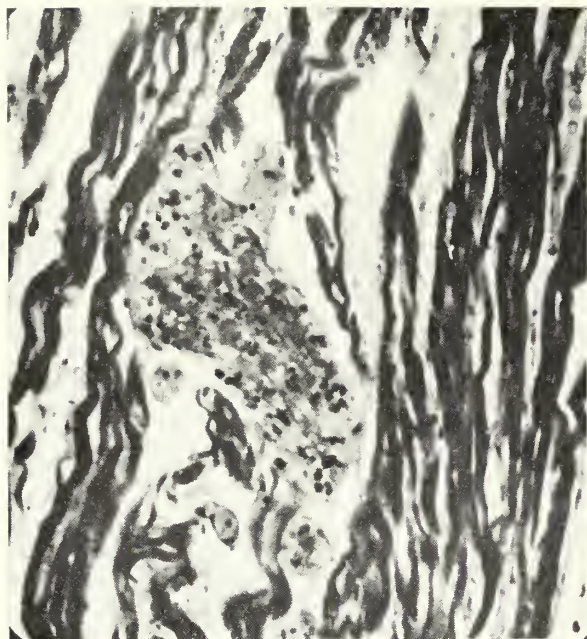


Fig. 6. Taken from the central zone of a control infarct, twelve hours old. Note the marked interstitial edema and deposition of fibrinlike material, with platelet aggregation in the capillaries and shrunken muscle fibers.

ment. This is a section of the central zone and exhibits moderate interstitial edema and some focal necrosis of muscle cells with leukocytic invasion. Note the absence of thrombi, hemorrhage, and vascular congestion.

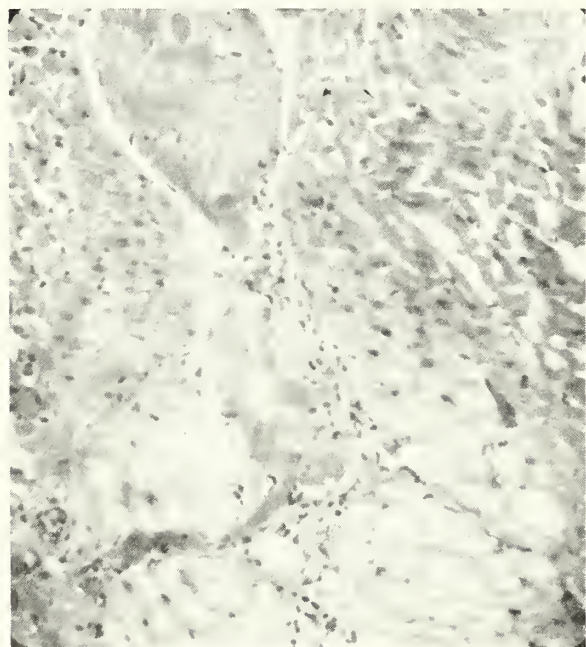


Fig. 7. Microscopic appearance in the peripheral zone of a twelve-hour control infarct, demonstrating microscopic thrombi in arterial and venous capillaries.

SUMMARY AND CONCLUSIONS

These experiments have demonstrated that it is possible to dissolve clots in the coronary arteries through the systemic administration of plasmin or streptokinase. Of greater importance is the limitation of the size and type of infarction in the treated, as opposed to the control groups following occlusion of the coronary artery for three hours. These differences are frequently striking and the absence of microthrombi both in the marginal and in the central zones suggests that this viability of the myocardium following interruption of its blood flow is due to preservation of the collateral circulation in the peripheral zone of the infarct. Inasmuch as we have shown that blood draining from an area of a myocardial infarct contains thromboplastin, which increases blood coagulation, it is possible that the explanation of these results lies in the fact that fibrinolytic therapy quickly dissolves fibrin deposits in the microcirculation at the peripheral zone.²⁵ This dissolution prevents self-extension of the infarct and helps preserve the collateral circulation of the myocardium deprived of its blood supply.

The clinical implications of this are obvious. Notably it appears that dissolution of the clot in a coronary artery following experimental myocardial infarction is of much less importance than the preservation of the circulation in the

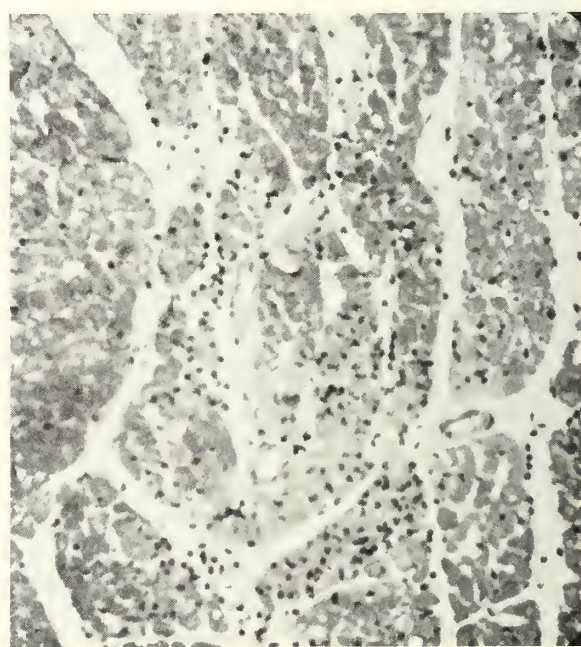


Fig. 8. Taken from the central zone of a plasmin-treated dog. Note the insignificant edema and the absence of microthrombi.

periphery of the myocardium deprived of its blood flow. This suggests that the objective in treating a patient with acute myocardial infarction should be the preservation and maintenance of the circulation in the marginal zone of the infarct rather than the dissolution of the clot in an atherosclerotic vessel. It also suggests that if treatment is begun within two or three hours following the vascular accident, limitation of the size of the infarction may be possible. Of secondary benefit might be the actual dissolution of the clot in the occluded vessel and the availability of this vascular tree for later collateral circulation.

Intramyocardial hemorrhage or myocardial rupture was not observed in any of the dogs treated with plasmin or streptokinase, despite the attainment of euglobulin levels of less than one hour.

It is our impression that the administration of presently available thrombolytic agents to patients is as yet premature. Commercially available fibrinolytic agents vary from batch to batch, both with regard to activity and to toxic properties, and it has been demonstrated that one commercial preparation produced no significant fibrinolytic action in vivo in the recommended dosage, despite reports of its clinical value in the therapy of thromboembolic disease.²⁶ Moreover, there is, as yet, no simple test, such as the prothrombin time, to register or measure the degree of fibrinolytic activity and, until such a test is available, treatment must be haphazard in certain respects, even with frequent determinations of euglobulin times. Finally, the general adoption of this form of treatment depends upon the development of a pure, nontoxic, synthetic activator. Streptokinase or streptokinase activated plasminogen may produce hypothermia or shock and, certainly, if given in excessive amounts, serious hemorrhagic complications. Furthermore, antistreptokinases are present in many individuals and must be measured in order to determine the priming dose of streptokinase. Subsequent treatment will be limited by the development of antistreptolysin titers in patients given these agents. The clinical evaluation of the efficacy of fibrinolytic agents in the treatment of acute myocardial infarction must await the collection and study of clinical, laboratory, and autopsy data from hundreds of patients under fairly rigid control—much more rigid than that exercised in the "Joint Study" undertaken in the evaluation of anticoagulant therapy.²⁷

The experimental data presented, however, give theoretic support to a program of controlled

administration of thrombolytic agents to patients who have sustained an acute myocardial infarction in the hope that such therapy may limit the size of the infarct as well as promote collateral microcirculation.

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The Implantable Cardiac Pacemaker

Present Status in the Treatment of Complete Heart Block with Adams-Stokes Syndrome

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THE DEVELOPMENT of methods for direct implantation of electrodes into the myocardium with an electrical pacemaker has completely revolutionized the treatment of complete atrioventricular dissociation.^{1,3}

The importance of this concept lies not in the fact that every patient with complete heart block necessarily needs electrical assistance but rather in the fact that those in whom conventional methods of therapy have failed or proved ineffective can now frequently be saved from sudden death and be rehabilitated, often dramatically, depending upon their age, myocardial reserve, and general state of health.

ETIOLOGY

Complete atrioventricular block may be produced by a variety of causes. These are listed as follows: (1) direct injury during intracardiac surgery; (2) congenital lesions—imperfect development of the bundle may be associated with atrial or ventricular septal defects or occur as an isolated defect; (3) inflammatory or degenerative lesions due to rheumatic disease, syphilis, tuberculosis, diphtheria, typhoid fever, pneumonia, or nonspecific myocarditis; (4) metastatic nodules; (5) formation of areas of fibrosis—most common etiologic factor and results from coronary sclerosis; this may be found in patients with coronary disease and/or systemic hypertension; (6) drug toxicity to digitalis, quinidine, and related compounds; and (7) etiology undetermined—no visible lesions.

The clinical response of the patient to complete heart block depends on the acuteness of

its development, the rate of the heart after the block has appeared and the metabolic needs of the body at the time. If the block is high in the bundle, the residual rate may be near normal or sufficiently rapid to maintain adequate flow. However, most often, chronic heart block is associated with bradycardia. The inherent rate of the idioventricular pacemaker, for example, is usually between 20 and 40 beats a minute, sometimes slower. Obviously, below a critical rate, the minute volume of blood flow is insufficient to meet the metabolic needs of the cerebral cortex, resulting in dramatic consequences, such as the appearance of syncope and convulsions, the familiar Morgagni-Stokes-Adams syndrome, or in fatal ventricular fibrillation because the heart itself may not have received sufficient blood.

PROGNOSIS

Complete atrioventricular dissociation, with the possible exception of the relatively rare congenital variety, invariably seriously impairs cardiac function and without active treatment has been associated with very significant morbidity and a very high mortality. Penton, Miller, and Levine,² reviewing the clinical features of complete heart block in 251 patients with blocks of diverse etiologies, found that the average duration of life after the first appearance of complete block was only 26.2 months. Congestive heart failure was present in 40 per cent of their cases. In this regard, it should be emphasized that the cardiac decompensation may, of course, be due to the primary etiologic factor producing the block but also may frequently occur as the sole result of a very slow rate and an insufficient cardiac output with an otherwise completely intact myocardium. This is an important consideration and may be an indication for surgical treatment in the absence of cerebral complications.

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Most patients with complete heart block have a serious bradycardia and, thus, require either medical or surgical therapy.

The primary aim of treatment is to maintain a rate sufficient to provide an adequate cardiac output. Some compensation with time is provided by the fact that the normal physiologic response to bradycardia is increased cardiac filling during the prolonged diastole, and, thus, an increase in cardiac size and stroke output occurs. In acute block, some increase in output may occur at once due to cardiac dilation, but considerably more time is necessary for further increase from cardiac hypertrophy, further dilation, stretching of the pericardium, and other compensatory mechanisms. Also, the primary condition responsible for the heart block, such as diffuse coronary disease or myocardial fibrosis, may seriously impair this natural compensation. However, even at best, it is evident that these natural compensatory mechanisms are often inadequate as attested to by the high morbidity and mortality of the condition referred to previously.

Pharmacologic agents. A wide variety of drugs have been used and advocated for treatment of complete heart block. This fact testifies to their limited effectiveness, particularly in some patients, and also to the fact that a certain medication may be specific in one instance, such as use of cortisone for complete heart block secondary to an allergic myocarditis, and of no value in another, such as transection of the bundle secondary to intracardiac surgery.

It is not our desire to review here the medical therapy for complete heart block with bradycardia but rather to emphasize several facts of importance which are derived from our personal experience in treating heart block patients pharmacologically.

Aside from the few medications which might have a specific effect upon the etiologic factor responsible for the block, by far the most valuable compound has been Isuprel (isoproterenol). Isuprel owes its beneficial effects to the fact that it specifically increases myocardial irritability, which is opposite in effect to digitalis, with relatively few undesirable side effects, and thereby the inherent idioventricular rate may be increased to an adequate level both by an increased rate and an increased contractility brought about by the increased muscle tone.

Some measure of the effectiveness of Isuprel may be derived from our earlier experience. In 1954, when intracardiac surgery for ventric-

ular septal defects first became possible, we were agreeably surprised to find that, contrary to some predictions, complete heart block did not occur with every operation but rather in only 10 to 15 per cent of our patients. However, we were quickly dismayed to find at that time that 100 per cent of our first 7 patients who sustained complete heart block succumbed in the postoperative interval. One and possibly 2 of these patients had other factors that might have been responsible for death, but, in the other 5, post-mortem examinations revealed a completely successful operative procedure anatomically and that death was clearly the result of an inadequate cardiac output, despite the fact that we had utilized all the methods for treatment then available, such as epinephrine, ephedrine, atropine, sodium lactate, and external electrical stimulation to the chest wall over the heart.

External electrical stimulation was of even less value in surgical patients than it has been in adults with block due to other causes. All of our patients at that time were children, and the pain associated with 75 to 100 volts applied 90 to 100 times per minute was intolerable. Because of these factors, it was not even possible to keep the electrodes in place long enough to get the skin burns from the electrodes that others have described. We also found that, because of the increased metabolic demands brought about by major surgery together with the acuteness of the block, death usually occurred if the cardiac rate dropped below 70 per minute for several hours or more; the mechanism of death in these cases was found to be cardiac arrest due to the development of metabolic acidosis, which occurred as a result of the inadequate output.

Isuprel was not utilized in these first 7 patients because only the linguets were available, and our patients were either too young or seemed unable to cooperate in keeping the tablets under their tongue in the early postoperative interval when the need was greatest. Likewise, we had not discovered the value of linguets administered rectally.

As this disappointing experience unfolded, we were able to obtain from the manufacturer an intravenous preparation of Isuprel for trial. This administered either intermittently ($\frac{1}{2}$ to 1 cc. in a 1:50,000 solution for adults, correspondingly less for children, every one-half to one hour) or by very dilute continuous intravenous drip proved to be the most effective drug available.

Shortly thereafter, we found that the Isuprel linguets were very effective if placed in the rectum. This route of administration produced an

effect beginning in fifteen to twenty minutes and lasting about two hours. This discovery greatly facilitated the use of Isuprel therapy by obviating the obvious problems of continuous intravenous administration for the prolonged intervals necessary. By these methods, the mortality of complete block in surgical patients fell from 100 per cent to 40 per cent, where it remained until early 1957 when the myocardial electrode was first utilized.³

Rectal Isuprel. Even in adult patients perfectly able to cooperate, the rectal route is often preferable because the effects are more reliable and more sustained.

We have had patients with complete heart block referred to us for surgical implantation of a myocardial electrode for Adams-Stokes attacks occurring while on sublingual Isuprel therapy rendered free of their cerebral symptoms by the simple expedient of switching them to rectal administration of their Isuprel linguets, 5 to 15 mg. every two to six hours.

We have demonstrated this increased efficacy of Isuprel administered rectally both by comparing the cardiac rate in the same patient in complete block with alternate methods of administration and, more dramatically, in several patients who had repeated Adams-Stokes seizures despite very frequent sublingual administration of Isuprel. In these same patients, simply changing the route of administration of the drug from



Fig. 2. Photograph of stainless steel coil-type electrodes used with the implantable pacemaker. The coil tip was developed to permit ingrowth of connective tissue to fix the electrode firmly in place.

sublingual to rectal with a lower total daily dose brought about an elevation of the heart rate to a level sufficient to give freedom from the seizures.

However, some patients may not respond adequately to any feasible dose of Isuprel or any other drug regardless of route of administration, and these patients are definite candidates for surgical treatment.

Surgical developments. Since introduction of the concept of direct myocardial stimulation with transistorized pacemakers and myocardial electrodes in patients with surgically acquired complete atrioventricular block, its use has been extended to nonsurgical patients with complete atrioventricular block.^{1,3}

With intensive efforts to further reduce the size of the components of pacemakers (transistors and long-lasting mercury cell batteries) together with advances in inert plastics and insulating materials, it has been possible to develop implantable pacemakers, the safety and reliability of which have made feasible the ambulatory treatment of patients with complete heart block.

Implantable pacemaker. This unit⁵ consists of the pacemaker itself and its 2 electrodes encased in silicone rubber⁶ (figure 1). An additional shorter extension of the unit containing

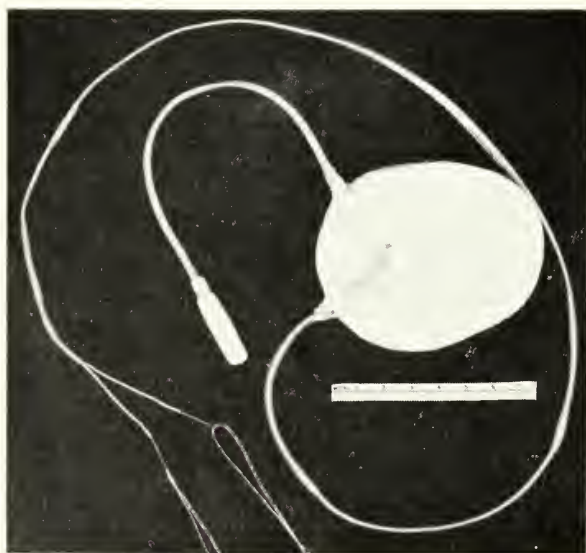


Fig. 1. Implantable pacemaker with long, stainless steel coil-type myocardial electrodes. Teflon sutures attached to electrodes are used in inserting electrodes into the myocardium. The shorter extension termed "pigtail" contains 3 wires, and a resistor is provided for emergency use in case of pacemaker failure. This complete unit is 6 cm. in diameter, 1½ cm. thick, and weighs 8 oz.

⁵Pacemaker manufactured by Medtronic, 3055 Highway 8, Minneapolis, Minnesota.

3 wires and a resistor (termed "pigtail") is provided for emergency corrective measures should pacemaker failure occur. Under such circumstances, the pigtail can readily be retrieved from its place under the skin, stripped of its silicone rubber coating, and attached to an external transistor pacemaker. The electrodes are of special design to resist breakage and to afford longer flex life (figure 2). The whole unit is gas sterilized, caution being taken not to exceed temperatures above 130° F. Cold sterilization can be utilized where gas sterilization facilities are not available.

Surgical technic. As patients with complete atrioventricular block are prone to have Adams-Stokes attacks at any time, and especially during the induction of anesthesia, it is our practice to attach an external pacemaker to the patient in his room prior to movement to the operating room and induction of anesthesia. This pacemaker is left at the standby position to be utilized immediately if necessary. For insertion of the internal pacemaker, the operation is begun by a left anterior thoracotomy through the bed of the fifth rib and by making a 2½-in. horizontal incision in the left lower quadrant at the level of the umbilicus and forming a pocket underneath the external oblique. The pacemaker inserted beneath the aponeurosis of the external oblique obviates seromas which may form with subcutaneous implantation, and, as it rests against the inguinal ligament, it does not drift downward pulling on the electrodes. The edge of the rectus sheath is then nicked, and, with



Fig. 4. Photograph of a patient showing healed incisions in left anterior chest and in left lower quadrant after implantation of pacemaker. (Case 3)

a long forceps, the leads of the pacemaker are brought up into the chest behind the rectus muscle. The electrodes are then attached to the left ventricle by threading each of the 2 stainless steel coil-type electrodes with a piece of Teflon† suture and threading this onto a Mayo needle and drawing it through a channel in the left ventricle, lateral to the left anterior descending coronary. Points of entrance of each electrode are secured in place with a 2-0 silk or Teflon mattress stitch tied over a tiny piece of compressed Ivalon. The Teflon stitches are then brought through the distal end through a small piece of compressed Ivalon pledget and then tied over it. A second spare set of electrodes of exactly the same design is also installed into the surface of the left or right ventricle in the same manner. The latter are brought through the chest wall above the thoracotomy incision and left coiled subcutaneously just outside the left pectoralis muscle underneath the nipple. The pericardium is then approximated over the points of insertion, the remainder being left open. The chest wall and abdominal incision are then closed in layers (figures 3, 4, 5, and 6).

Selection of cases. Indications for the use of the implantable pacemaker in all the cases herein reported were limited to those who were incapacitated, despite current forms of medical management, by both intermittent attacks of syncope and a cardiac output which consistently remained so low that useful work and physical activity had become impossible. The patients'

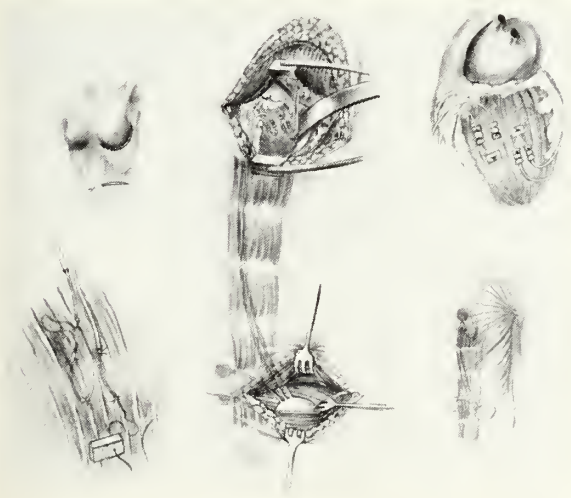


Fig. 3. Diagrams showing steps of surgical procedure used in implantation of pacemakers. Note subcutaneous position of pigtail in abdomen and spare set of electrodes to be used as corrective measures in case of failure.

†U. S. Catheter Co., Glens Falls, New York

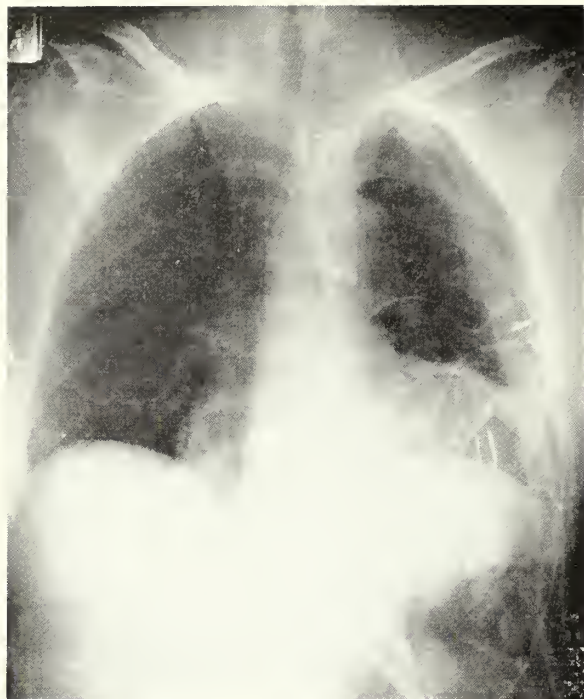


Fig. 5. Chest film of patient after implantation of the pacemaker. One group of electrodes is connected to pacemaker placed in left lower quadrant and is attached to left ventricle. A spare pair of electrodes is attached to right ventricle, brought through chest wall, and coiled subcutaneously to provide a safety measure in case of failure of the other electrodes.

ages were also considered an indication, as the average age at death in these patients is 63.2 years.² The ages of the patients here reported ranged between 59 and 83, with a mean age of 67.8 years. It may be emphasized here that younger patients with persistent complete atrio-ventricular block, congenital or acquired, are obviously much better candidates for internal pacemaker implantation than the elderly patients herein treated.

Since January 15, 1961, we have implanted internal pacemakers in 7 patients with complete atrioventricular block, Adams-Stokes attacks, and extreme physical disability (table 1). The case reports are as follows:

CASE REPORTS

Case 1. E. O., a 63-year-old white male, was admitted on January 15, 1961, for blackout spells and slow heart rate for the past two years. Blackout spells occurred about once a month on getting up and were not helped by Isuprel and Diuril. He was a very heavy smoker, having smoked 40 cigarettes a day for the past two years. Pertinent physical findings included blood pressure of 215/60 mm. Hg and a pulse rate of 26 per minute. Cardiac fluoroscopy showed cardiomegaly with slow activity. The electrocardiogram revealed complete atrio-ventricular block with idioventricular focus in the left

ventricle. On January 17, 1961, an internal pacemaker was implanted which fixed the heart rate at 60 per minute (figure 7). The procedure was uneventful, but a cerebral thrombosis developed on the tenth postoperative day; however, he improved from this rather quickly and was discharged on February 20, 1961, ambulatory and in good condition. He did well until September 21, 1961, when his pulse rate suddenly dropped to 30 per minute. He was hospitalized then for measurement of resistances and was attached to an external pacemaker by making a tiny incision under local anesthesia and exteriorizing the pigtail. On October 5, 1961, the internal pacemaker was reconnected by identifying the nonfunctional myocardial electrode and connecting it to an indifferent electrode which was then buried in the rectus muscle and the skin completely closed over the pigtail again. Healing occurred per primum, and his blood pressure was 110/70, and his pulse rate was again 58 per minute at the time of discharge.

Case 2. M. S., a 68-year-old white female, was admitted on March 31, 1961, with a history of repeated blackout spells and severe hypertension for four years. She decided against treatment by pacemaker implantation and was discharged on Isuprel therapy. She was readmitted on the next day, having had 10 attacks of syncope with convulsions during the interim. At the time of admission she was also found to be bleeding profusely from her upper gastrointestinal tract, and her blood pressure was at shock level. She responded well to treatment, which included 3,000 cc. of blood replacement. Her blood pressure was restored to 280/90; pulse rate varied between 33 and 60 with rectal Isuprel 15 mg. every two hours. Roentgenograms and upper gastrointestinal series



Fig. 6. Roentgenogram of abdomen showing implanted pacemaker in lower left quadrant, course of leads to heart, and position of pigtail. The unit contains 9 1½-volt mercury cells delivering a biphasic pulse of one milli-second at a rate fixed before implantation.

TABLE 1
PACEMAKER TREATMENT ADAMS-STOKES SYNDROME
COMPLETE IMPLANTATION

Case	Age (years)	Etiology	Syncopal episodes		Previous Rx	Cardiac response and late results
			Number	Duration		
E. O.	63	Myocardial infarctions	25	2 years	Ephedrine Atropine Isuprel	Excellent, 60 per minute
M. S.	68	Hypertension 280/90	30 (2 intracardiac episodes)	4 years	Diuril Cortisone Isuprel	Excellent, 58 per minute
J. L.	78	Hypertension 180/90 Diabetes	12	3 years	Diuril Isuprel	Excellent, 58 per minute
E. C.	66	Myocardial infarctions	20	3 years	Isuprel ACTH Decadron Atropine Diuril	Excellent, 56 per minute. Sudden death 3 months postoperatively due to infarction
L. F.	59	Myocardial infarctions Hypertension 180/80	30	1 year	Diuril Isuprel Ephedrine	Arrested 2 hours postoperatively. Resuscitated with complete recovery; rate, 72 per minute
F. D.	83	Hypertension 280-300/110	2	10 months	Isuprel Diuril	Sixty per minute. Cerebrovascular accident on third and eighteenth postoperative days. Death due to cerebrovascular accident
T. K.	59	Hypertension 200/70	Daily	2½ years	Isuprel Diuril	Excellent, 58 per minute

showed no gross pathology. Her heart shadow indicated left ventricular enlargement. An electrocardiogram revealed complete atrioventricular block with idioventricular focus in the left ventricle, left ventricular hypertrophy, and probably old atypical anterior myocardial infarction. On April 7, 1961, she was operated on for insertion of an internal pacemaker. Her heart rate was then fixed to a rate of 55 per minute. Blood pressure with this heart rate was 160/70. Recovery was uneventful. The patient was discharged on April 21, 1961, with activity to be increased as tolerated.

Follow-up examination on October 27, 1961, found her doing very well without medications.

Case 3. J. L., a 77-year-old white male was admitted on April 9, 1961, with a history of blackout spells every two to three months since 1957. Dyspnea and fatigability had been present since 1959. He had diabetes, which was controlled by diet and Orinase. On physical examination, he appeared to be in no distress. Blood pressure was 170/70, and pulse rate was 36 per minute and irregular. Roentgenograms showed moderate generalized cardiomegaly with pulmonary congestion and fibrosis. An electrocardiogram revealed complete atrioventricular block with an idioventricular rate of 40 per minute with frequent ventricular extra systoles. On April 14, 1961, an internal pacemaker was inserted, and his heart responded with a constant rate of 58 beats per minute. Postoperatively, his blood pressure fell to 118/74 with this increase in heart rate. His convalescence was uncomplicated. He was discharged on digitoxin and Orinase and told to engage in physical activity as tolerated.

Case 4. E. C., a 66-year-old white female, was admitted on April 26, 1961. In 1957, she had suffered 3 blackout spells. An electrocardiogram at that time revealed complete atrioventricular block with sinus rhythm occurring intermittently. She was therefore put on Isuprel, ACTH, and belladonna preparations. In 1958, she sustained a myocardial infarction. Since that time, she has

remained in complete atrioventricular block and able to engage in very limited physical activity. During the last several months her condition had deteriorated, and she had very frequent blackouts. Her blood pressure was 130/70 mm. Hg, and her pulse rate was 50 per minute and regular on Isuprel. She had slight ankle edema and a moon face with telangiectasia. Her electrocardiogram was consistent with complete atrioventricular block. On May 3, 1961, an internal pacemaker was inserted. The pacemaker rate was set at 58 per minute. Following surgery, her blood pressure was 110/64. Her recovery was uneventful. She was maintained on anticoagulant therapy following discharge.

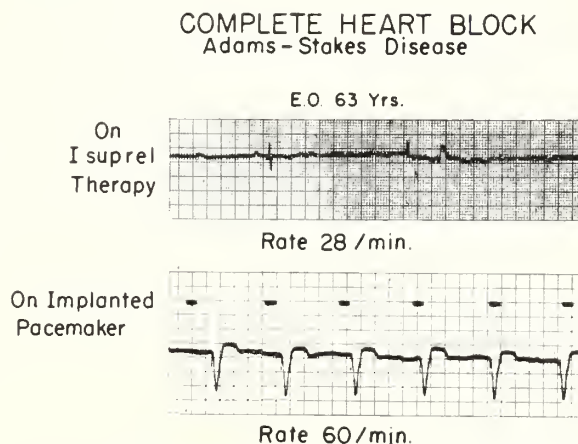


Fig. 7. Electrocardiograms of patient E. O. with complete heart block. Tracings made while patient was on Isuprel therapy and after implantation of pacemaker. The current drain is such that the estimated battery life of the implanted unit is 4 to 5 years and as the battery life is exhausted the pulse rate will gradually increase for several weeks, providing a useful warning sign.

The patient died suddenly on July 3, 1961, from a myocardial infarction.

Case 5. L. F., a 59-year-old white female, was admitted on July 17, 1961, with Adams-Stokes attacks and dyspnea on exertion. She was known to be in complete heart block since August 3, 1960, and she had her first blackout spell on September 25, 1960. She was treated with ephedrine, Isuprel, and Diuril but continued to have 1 to 2 blackout spells per month. Pertinent physical findings were obesity, blood pressure of 178/78 mm. Hg, pulse rate of 25 to 30 per minute, cardiomegaly on fluoroscopy, and complete atrioventricular block on electrocardiogram. On July 18, 1961, an internal pacemaker was inserted. The patient had an attack of ventricular fibrillation in the postanesthetic recovery room. She was resuscitated by external cardiac massage and external defibrillation. Following resuscitation, an electrocardiogram disclosed that the internal pacemaker was functioning satisfactorily, driving the heart at a rate of 72 per minute. Her blood pressure remained around 114/70 mm. Hg. The etiology of the ventricular fibrillation immediately postoperatively remained obscure. She recovered uneventfully and was discharged on August 1, 1961. One month after surgery, her pulse rate was noted to be 37 per minute. She had an Adams-Stokes attack on the day prior to her second admission, which was on August 24, 1961. The previously placed extra set of electrodes was retrieved from their subcutaneous position in the chest wall and attached to an external pacemaker and the internal pacemaker was removed. At the time that this patient developed difficulty with her pacemaker, methods for splicing the electrodes had not been developed. Methods have subsequently been worked out and were applied successfully in patient E. O. Patient L. F. was doing well utilizing the transistorized external pacemaker¹ when last seen on November 13, 1961.

Case 6. F. D., an 83-year-old white male, was admitted on July 23, 1961, with complaints of "feeling weak on walking." He had had 2 blackout spells eight and ten months before and severe hypertension with a blood pressure of 280 to 300/110 mm. Hg. He had been treated with Isuprel and Diuril but had continued to maintain his pulse rate between 29 and 40 beats per minute. On physical examination, his blood pressure was 300/80 mm. Hg, and his pulse rate was 48 per minute. He had cardiomegaly, a grade III systolic murmur at the apex, and ankle edema. A roentgenogram showed a left ventricular configuration. The electrocardiogram revealed complete atrioventricular block. On July 27, 1961, an internal pacemaker was implanted which drove the patient's heart at 58 beats per minute. His blood pressure was reduced to 180/100 mm. Hg. Three days after surgery, he suffered a cerebrovascular accident, which left him with impaired ability to swallow and in a state of confusion. He gradually improved until August 14, 1961, when he suddenly collapsed. Resuscitative measures were of no avail, although the heart rate remained at 58 per minute.

Postmortem examination revealed that the immediate cause of death was a cerebrovascular accident. The pacemaker and electrodes were intact with no detectable malfunction.

Case 7. T. K., a 59-year-old white male, was admitted on October 10, 1961, with a history of daily dizzy spells for the last two and one-half years. He had been treated with Diuril and Isuprel without relief of his symptoms or elevation of his pulse rate above 30 to 35 per minute.

He had been unable to work for the last one and one-half years. His left kidney had been removed in 1952 because of chronic infection and hydronephrosis. His blood pressure was 210/74 mm. Hg, and his pulse rate was 28 per minute. His roentgenograms showed cardiomegaly, and the electrocardiogram revealed complete atrioventricular block. An internal pacemaker was inserted on October 17, 1961. The pacemaker rate was set at 58 beats per minute. The patient made an uncomplicated recovery and was discharged on November 6, 1961. His blood pressure since surgery has remained at 140/70 mm. Hg.

COMPLICATIONS

Of the foregoing 7 patients, cerebrovascular accidents developed in 2 in the early postoperative period (E. O. and F. D.). A second cerebrovascular accident in 1 patient (F. D.) and accounted for his death. Ventricular fibrillation developed in 1 patient (L. F.) in the postanesthesia recovery room, but she was successfully resuscitated. In 2 patients (E. O. and L. F.), failure of electrical stimulation occurred due to increased resistance that developed in the electrodes one month and eight months after insertion. These were readily identified, and the pigtail in 1 patient and the previously inserted spare electrodes in the other were utilized without event. In 1 patient (E. O.), the control of the heart rate by the implanted pacemaker was restored after the nonfunctioning electrode was connected* at the pigtail to an indifferent electrode which was then placed into the adjacent muscle and the tiny skin incision above the umbilicus closed. This procedure was carried out under local procaine anesthesia and the wound healed per primum.

Employing the technics described, we have had no cases of infection develop following pacemaker implantation.

COMMENTS

In complete heart block, the ventricles are extremely responsive to electrical stimulation of small magnitude, such as that delivered by the transistor pacemaker via an electrode implanted in the myocardium.

Direct myocardial stimulation increases the low cardiac output, which is due to the slow heart rate of complete atrioventricular block, and thus ameliorates fatigue, congestive heart failure, fainting spells, and convulsive seizures. The occurrence of asystole for longer than twenty seconds is prone to terminate in fatal ventricular

*The wires were joined by solderless Krimp Connector (No. 34070C, American Pacmor, Inc., Havertown, Penn.) and the connection then sealed with medical adhesive silicone rubber (type A, room temperature curing, Dow Corning Co., Midland, Michigan). The silicone rubber was allowed to cure for 45 minutes exposed to room air and temperature and then buried in the subcutaneous tissues.

TABLE 2
EFFECT OF PACEMAKER IMPLANTATION UPON
SYSTEMIC BLOOD PRESSURE IN PATIENTS
WITH COMPLETE BLOCK

Patient	Age (years)	Sex	Average pulse rate and blood pressure			
			Before	After	Before	After
E. O.	63	M	30 to 35	58	215/60	110/70
M. S.	68	F	40	58	280/90	160/70
J. L.	78	M	30 to 35	58	170/70	118/74
E. C.	66	F	45	60	130/70	110/64
L. F.	59	F	25 to 30	72	180/80	114/70
F. D.	83	M	29 to 40	59	280 to 300/110	180/100
T. K.	59	M	28	58	200/70	140/70

fibrillation due to myoeardial anoxia. The patients not only regain physical ability and emotional relief but also are freed from fear of sudden death when the cardiac rate is controlled by the pacer.

The 7 cases reported were all in the advanced age group. Their refractoriness to medical treatment and recurring Adams-Stokes attacks indicated their poor prognosis. All considered, the results obtained by implantable pacemaker stimulation in these patients are very encouraging. Palliation, with comfortable living, if not an alteration of the natural course of their underlying arteriosclerotic disease, was definitely achieved.

As indicated before¹ and as our experimental data have confirmed, a failing heart from anoxia or many other causes will not respond to electrical stimulation. If indications for pacemaker control of complete atrioventricular block are extended to patients before undue delay for medical therapeutic trials has elapsed, a better response of the heart to artificial stimulation may be expected in this still compensated stage. Several of our patients had had congestive heart failure before surgery and were considered for pacemaker stimulation only as a last resort.

The severity of the underlying arteriosclerotic arterial and heart disease in these older patients obviously has an important role in determining the long-term prognosis once the complications of the disease secondary to complete atrioven-

tricular disassociation, low cardiac output, and Adams-Stokes attacks are controlled successfully by the implanted pacemaker.

Following insertion of the pacemaker, in addition to the marked symptomatic relief and emotional rehabilitation in these patients, a dramatic lowering of blood pressure toward desirable levels occurs (table 2). This reduction in blood pressure was achieved through a reduction of the stroke output into rigid arteriosclerotic systemic vessels and the fact that sympathomimetic drugs, such as ephedrine, Isuprel, etc., could be discontinued. This fact, when viewed with respect to the progressive nature of the disease, suggests the advantage of earlier selection of cases for pacemaker treatment.

SUMMARY

The present status of the use of implantable pacemakers for the treatment of complete atrioventricular dissociation is discussed. Implantable pacemakers were used in 7 patients with complete atrioventricular dissociation and Adams-Stokes attacks refractory to medical management. Surgical technique, case histories, complications, and comments on control of symptoms in patients with complete atrioventricular dissociation by implantable pacemakers are discussed.

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Hypertension Secondary to Congenital Stenosis of the Renal Artery

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OVER ONE HUNDRED YEARS have passed since Richard Bright¹ first described the association of renal disease with cardiac hypertrophy and fullness of the pulse, but the precise relationship of the kidney to arterial hypertension remains incompletely understood. That reduction of the lumen of the renal artery plays a role in the establishment of hypertension became apparent from the efforts of Katzenstein² in 1905 and Carrel³ and Janeway⁴ in 1909. But, in all of these early experiments carried out in dogs, the hypertension was transient in nature.

The marked sclerosis of the arteries and arterioles observed by Ask-Upmark⁵ in the renal parenchyma of patients dying of malignant hypertension likewise emphasized the importance of the renal vasculature in the genesis of hypertension. Yet, not until the classic work of Goldblatt and associates⁶ in 1934 was there solid experimental confirmation of these earlier observations. They were able to obtain relatively permanent hypertension in animals by partial occlusion of the renal artery with a screw clamp. A return of blood pressure to normal was achieved by either removing the clamp or the involved kidney.

PATHOLOGIC PHYSIOLOGY

On the basis of these observations, Blackman⁷ in 1939 suggested that atherosclerotic plaques in the renal arteries of patients dying of hypertension might, indeed, be the cause of hypertension in such individuals. The proposition that renal ischemia was the initiating mechanism in the production of arterial hypertension was given further support by the studies of Talbott and associates,⁸ who in 1943 observed that any measured reduction in renal blood flow, as determined

by clearance methods, was directly related to the severity of the renal vascular changes.

In 1940, Braun-Ménendez and co-workers⁹ and Page and Helmer¹⁰ independently concluded that renin, a substance present in renal vein blood, acted on a plasma globulin to form hypertensin, a potent vasoconstrictor agent. These original inferences have been modified, and the current belief is that renin, a proteolytic enzyme, splits a polypeptide from a protein substrate synthesized by the liver. This polypeptide, a decapeptide, is in turn acted upon by another enzyme in blood, resulting in the release of histidyl-leucine. The resulting octapeptide, called angiotensin, is the vasoconstrictor agent. The exact mechanism by which renin is released is as yet unknown. Kohlstaedt and Page¹¹ in 1940 were able to secure the release of renin without the production of renal ischemia, while DeCamp and Birchall¹² have suggested that a diminution of pulse pressure in the renal artery is responsible for the renin release by the kidney. The clearance studies of Morris and associates¹³ revealed a minimal reduction of renal blood flow in patients with severe renal artery obstruction.

Grollman and co-workers¹⁴ in 1949 proposed the alternate thesis that lack of a renal antipressor agent might in fact be responsible for hypertension of renal origin. The experiments of Kolff and Page¹⁵ in 1954 gave additional support to the occurrence of such an agent; they showed that the hypertension observed in bilaterally nephrectomized dogs maintained by peritoneal dialysis was ameliorated by transplantation of a normal kidney into such an animal.

The altered excretory function of the ischemic kidney was observed in 1951 by Mueller and associates.¹⁶ They noted that renal artery obstruction in the dog produced a decrease of urine flow and urinary sodium concentration from the involved kidney. Subsequently, Howard and co-workers¹⁷ verified these observations in human beings with renal artery obstruction.

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Dustan and associates¹⁸ in 1959 reported that clearances of both inulin and para-aminohippurate were depressed in human beings with renal artery obstruction.

PATHOLOGY

Renal artery. Congenital intrinsic renal artery obstruction has occurred either with coarctation of the abdominal aorta, in which case the renal artery or arteries are typically coarcted at their origins from the aorta, or as a distinct entity, in which the obstruction was almost always due to fibromuscular thickening of the media and intima with consequent narrowing of the lumen of the artery. Whether or not a particular case of the second type is truly congenital or acquired may be impossible to say. Several cases^{12, 19-25} of the second type have been reported in patients under the age of 20, and, in these, a congenital origin appears to be more likely. For other patients^{13, 25-27} in their third and fourth decades, virtually identical histologic arterial changes have been described, and uncertainty exists for them, since, as a group, they fall well into the age in which "essential hypertension" appears. Too, for these older patients, hypertension has generally been observed for relatively brief periods; therefore an acquired lesion might be deemed a more probable cause. Their intimal and medial arteriolar changes have been termed juvenile atherosclerosis or atherosclerosis praecox.

Renal parenchyma. Wilson and Pickering²⁸ in 1938 pointed out that in experimental hypertension due to renal artery obstruction, the renal vasculature distally placed is "protected" from the high systemic pressure and these conduits, therefore, remained histologically normal, while arterioles in the nonobstructed kidney developed fibrinoid and hyaline degeneration and necrosis of the walls. To a corresponding degree, tubular atrophy, degeneration, and necrosis were more likely to be observed only in the nonobstructed kidney. Yuile²⁹ in 1944 confirmed these observations in patients dying of hypertension due to atherosclerotic obstruction of the renal artery.

DIAGNOSIS

The importance of a thorough investigation of hypertension in the pediatric age group has been emphasized by Snyder and associates³⁰ and Poutasse,³¹ since an organic basis for such hypertension commonly exists. Widespread agreement exists that aortography is the single best adjunct in the precise diagnosis of renal arterial obstruction. However, simpler procedures should be utilized first as a screening device or case-finding technic.

The simplest of these procedures is intravenous urography. Dustan and co-workers¹⁸ described the features to be sought in their large series of patients. In most patients with renal arterial obstruction, a decreased concentration of radiopaque material is present on the involved side and this kidney is generally smaller. Retrograde urography has also proved valuable in distinguishing renal arterial from renal parenchymal disease. In the former, the calyces are usually small but of normal configuration, while, in the latter, blunting of the calyces is noted when pyelonephritis is the underlying cause.

Differential renal function studies have been described by Howard and associates.¹⁷ Dustan and co-workers¹⁸ and Morris and associates¹³ have described changes in differential inulin and para-aminohippurate clearances. Inulin clearance on the side of the arterial lesion is invariably depressed along with para-aminohippurate clearance. Rapoport³² has modified the "Howard" test and emphasized the inverse creatinine concentration in urine under these conditions. However, these differential renal function studies are recognized to be nonspecific for renal arterial obstruction, since similar aberrations can occur in other types of renal parenchymal disease.¹⁸

Another diagnostic test is the radioactive renogram, which was introduced by Winter²⁴ in 1957 and employs either radioactive Diodrast or Hippuran. Following an intravenous injection of one of these tracers, external bilateral flank measurements for the isotope are made. A lower count is found over the abnormal kidney. From the curves obtained, renal parenchymal disease can at times be distinguished from renal arterial obstruction.

THERAPY AND RESULTS

An initial effort to cure hypertension of renal origin was made by Butler³³ in 1937. He reported an apparent cure after nephrectomy in a patient with unilateral pyelonephritis. This resulted in a wave of enthusiasm for that procedure, and, in 1956, Smith³⁴ collected reports of 575 nephrectomies carried out for hypertension which was suspected to be due to unilateral renal disease. However, only 26 per cent of this group was benefited by the procedure. Doubtless, a number of cases of renal artery disease lie buried in this group, for, in many cases, the state of the renal arteries was not described or, in fact, known.

With the advent of more accurate diagnostic measures and improved vascular technics, emphasis in surgical treatment shifted to a direct attack on the renal artery, and, in 1954, Freeman

and associates³⁵ were able to report a cured case of hypertension due to atherosclerotic obstruction of a renal artery treated by endarterectomy. Poutasse²¹ in 1956 was similarly able to effect a cure by the use of bilateral aortorenal bypass homografts in a 15-year-old boy. The following year Winter²⁴ reported excision of an isolated congenital stenosis of a renal artery, and, in 1958, Parton and Nabeth³⁶ performed an end-to-side splenorenal arterial anastomosis for an atheromatous obstruction of the renal artery. To date, 138 patients^{12, 13, 18-27, 31, 35-42} have been reported to have had direct operations on the renal arteries, but only 9 patients could *definitely* be said to have had a congenital lesion, while 23 other patients *might* have had a congenital stenosis. The remaining 106 patients all had atheromatous lesions of the renal artery.

CASE REPORT

The following case appears to qualify as that of a congenital lesion, particularly in view of the associated coarctation of the superior mesenteric artery and despite the lack of antecedent hypertensive history.

R. M., a 23-year-old male, had enjoyed good health and presumably had a normal blood pressure until significant hypertension was identified late in 1958 and reconfirmed early in 1959. For this the patient was given Eskaserp, but he continued to have headaches and to become easily fatigued. The medication did little to restore his blood pressure toward normal in a brief trial. In October 1960, he was again given reserpine, but the blood pressure continued to rise slowly and steadily. It also was not influenced by hydrochlorothiazide supplemented with potassium. His blood pressure measurements ranged up to 200/140. Retinal funduscopic examination at that time revealed mild generalized arteriolar narrowing but no hemorrhages, exudates, or papilledema. His electrocardiogram and chest roentgenograms were interpreted as within normal limits.

The patient was thoroughly studied in order to identify the mechanism of his hypertension that was apparently of recent development. Femoral pulses were found to be full bilaterally. Urinalysis was essentially normal. An intravenous pyelogram was normal. The blood urea and creatinine levels were normal. The phenolsulfonphthalein excretion was normal. Serum electrolyte determinations were all essentially normal. A Regitine test was negative. Urinary catecholamine excretion was normal. The patient's Howard-Rapoport test was positive, with decreased volume and sodium excretion from the right kidney and increased creatinine excretion from the right kidney in each case as compared with the left. A selective renal arteriogram was carried out via the right femoral artery on March 1, 1961. The catheter was inserted into the region of the orifice of the right renal artery, and subsequent radiopaque dye injection revealed a severe stenosis of the right renal artery, poststenotic dilation, and delayed nephrographic delineation of the right kidney as compared with a prompt and (perhaps) enhanced compensatory response from the left kidney.

In addition, it seems likely that this patient had other congenital malformations of the vascular branches of the abdominal aorta.

With this diagnosis of congenital renal arterial stenosis, he was operated upon April 18, 1961. At that time, dissection of the aorta revealed a high grade, virtually complete coarctation at the origin of the right renal artery and, in addition, a severe coarctation of the superior mesenteric artery. This area of renal arterial coarctation was virtually flush with the take-off of that structure. Under these circumstances, it was technically easier to divide the renal artery at its origin and reanastomose it to the side of the aorta at a somewhat more distal site. This arrangement permitted establishment of a widely patulous lumen, which was approximately 7 mm. in diameter and slightly wider than the adjacent distal artery. Following release of the vascular clamps, a full pulsatile flow was promptly established. This had been completely absent beforehand from the right renal artery. Biopsies of both kidneys were done at the time of surgery. The right kidney, site of the congenital renal artery stenosis, exhibited normal microscopic vascular architecture. In contrast, the "unprotected" left kidney revealed definite, though moderate, arteriolosclerotic changes. The patient's convalescence from the operative procedure was without event.

He continued, however, to maintain hypertensive blood pressure levels while in the hospital, but, during the succeeding months, these values have declined and, upon the last two visits to the clinic in August and October 1961, the blood pressure has been not measurably higher than 140 systolic and the diastolic has ranged around 80 to 90. In addition, he is currently completely free of his former symptoms of headache and easy fatigability, although he is working vigorously at fairly heavy physical activity.

SUMMARY

In general, excellent results have been reported in the overwhelming majority of patients undergoing direct arterial surgery. In 1961, Morris and associates²⁶ reported that 82 per cent of 75 patients who underwent direct arterial surgery had a return to normal blood pressure values after operation, while the remaining 18 per cent showed a reduction in blood pressure, though not to normotensive levels. Although the less favorable results of direct arterial surgery have probably not been reported, such operations appear to hold great promise for the small percentage of patients with hypertension caused by renal artery disease. In this case, this young man may well be cured.

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This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.

IN NEONATES, high doses of chloramphenicol may be fatal. After a few days of such therapy, signs of vascular shock suddenly appear and death follows within two to seventeen hours. When any sudden outbreak of early neonatal deaths occurs, drug toxicity as well as infection should be suspected. Of 12 infants given more than 110 mg. of chloramphenicol per kilogram of body weight per day for prevention or treatment of suspected infection, 9 died at 2 to 5 days of age after sudden vascular collapse. Investigation strongly suggested that the fatalities were due to chloramphenicol intoxication.

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Book Reviews . . .

Atlas of Obstetric Technic

J. ROBERT WILLSON, M.D., 1961. *St. Louis: C. V. Mosby*. 304 pages. Illustrated. \$14.50.

This unique atlas is designed to provide detailed descriptions and illustrations of the common obstetric procedures rarely included in our standard textbooks. The author assumes that the reader will have had professional background preparation in obstetrics and that this book will supplement his knowledge and practice of obstetric techniques.

The introductory chapters discuss briefly staff organization, delivery room facilities, and personnel. The author stresses the importance of efficient planning in good obstetric practice. The conduct of normal labor and delivery is described in some detail. Particular emphasis is placed on the proper management of the vexing problem of shoulder dystocia and the placental stage. Forceps delivery is presented in great detail. Chapters on breech delivery, version, and abdominal delivery follow.

Each procedure is described step by step in a clear, concise, lucid manner on one page and illustrated in great detail by black-and-white drawings on the opposite page. Dr. Willson is fortunate to have Daisy Stilwell witness these procedures in the delivery room and on the manikin and skillfully reproduce them in the text. The clarity of these illustrations will be appreciated by the graduate student in obstetrics as well as the practitioner, who is responsible for much of the obstetric practice in our country.

This book by Dr. Willson, who is one of our outstanding teachers and clinicians, should be available in the physician's study and in every labor ward where standard procedures can be reviewed and practiced by students and practitioners.

M. EDWARD DAVIS, M.D.
Chicago

Health Education: A Guide for Teachers and a Text for Teacher Education

BERNICE R. MOSS, WARREN H. SOUTHWORTH, and JOHN L. REICHAERT, editors, fifth edition, 1961. *Washington, D. C.: National Education Association of the U.S.* 429 pages. Illustrated. \$5.00.

The stated purpose of this book, a project of the Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association, with the cooperation of contributors and consultants, is to assist all persons concerned with health education in the school. It represents a completely rewritten fifth edition of a book which was first published in 1924.

Only when the school, home, and community are interrelated can the full potential of health education be realized. This, of course, includes the physician serving the school and the physician serving the school-age child. A cursory glance at the table of contents of this book may give the busy physician the impression that the book is of primary interest to educators. However, the average physician will be much better prepared to play his important role in his local school health program if

this book is in his collection. Although he will be particularly interested in chapter 13—"Health Services and Healthful School Living as Sources of Health Education Experience"—the entire book would be worth reading, particularly if his duties include serving part or full time as a school or college physician.

The many educators, physicians, nurses, and others who contributed to this publication are to be congratulated in providing another stimulus to improved health education. Of course, teacher-training institutions will find it invaluable as a text or reference in the training of all teachers.

JOSIAH G. NEAL
St. Paul

Minds That Came Back

WALTER C. ALVAREZ, M.D., 1961. *Philadelphia: J. B. Lippincott*. 384 pages. \$5.95.

Dr. Alvarez has made a unique and important contribution to the study of the mentally disturbed individual. Those of us who have known Dr. Alvarez have recognized his deep interest in the problems of the emotionally disturbed and the mentally ill. During these years, he has collected biographies of many famous people who were judged insane. There is no question that these people were mentally unbalanced. With his usual brilliant analysis and selection of material, he emphasizes that many of these individuals returned to a normal life. It is also interesting that many persons who are actually insane are able to carry on a normal community life. Dr. Alvarez's many contributions to this field of medicine have reinforced the fact that all practitioners must be aware of the influence that mental and emotional states have upon the individual's well-being.

The book is well printed and well designed. The material is ably selected. It should be in the hands of everyone who in any way is engaged in the care of people. Dr. Alvarez is to be congratulated on what may prove to be the greatest of his many great contributions to medicine.

JOHN F. BRIGGS, M.D.
St. Paul

The Practitioner's Handbook

WILLIAM A. R. THOMSON, M.D., editor, 1961. *Philadelphia: J. B. Lippincott*. 711 pages. Illustrated. \$12.50.

In this volume there are no chapters, as such, and only half a dozen illustrations. One finds instead 700 pages of solid reading matter on roughly 250 topics, ranging from "Infant Feeding" at the beginning of the book to "Night Cramp in the Elderly" toward the end. Each topic discussed varies in length from 1 to 5 pages.

The volume is an outgrowth of a series of articles published in *The Practitioner*. Each piece is intended to cover some practical problem encountered by the general practitioner.

The book does not assume to give the latest information on drug research or on progress in pathologic procedure. It aims rather to provide concise but authoritative reviews on diagnostic methods and treatment programs which have proved most reliable in clinical practice.

The 200 contributors to the volume discuss such varied

BOOK REVIEWS

topics as "The Child Who Won't Eat," "The Use and Abuse of Eyedrops," and "The Treatment of Tics." In the discussion on the topic "The Sore Tongue" we spot this little gem in explanation of its sometime condition: "it wags enough and works enough to suffer from wear and tear."

As a handbook of diagnosis and treatment of many of the problems facing the general practitioner from day to day, I think this volume may be of considerable help.

The index is the key to this book and is necessarily voluminous. Because of the nature of the book, it can be recommended as a quick and handy guide on a large number of clinical topics, as well as on some behavior problems.

REUBEN F. ERICKSON, M.D.
Minneapolis

Radiopaque Diagnostic Agents

PETER K. KNOEFEL, M.D., 1961. *Springfield, Ill.: Charles C Thomas. 113 pages. Illustrated. \$6.75.*

This is an important contribution covering the character and use of radiopaque chemicals designed for visualization of body parts. The volume includes physical and optical considerations and a detailed evaluation of various compounds used for visualizing the alimentary tract, the biliary system, the urinary system, the circulatory system, the respiratory tract, the spinal subarachnoid space, the genital tract, and the reticuloendothelial system. The diagnostic procedures themselves are appraised, and special attention is given to the potential toxicity of the substances used. Most of the compounds involved contain iodine, which is why so many radiopaque diagnostic agents are expensive.

This volume has been greatly needed. It summarizes the current information, gathered from 359 references, on an increasingly important type of drug, namely, that used for diagnosis. Professor Knoefel gives the essential information about the wide variety of radiopaque diagnostic compounds, listing in an appendix the 17 major types and offering in another appendix the published data on the lethal toxicity of these compounds on single dose in experimental animals. Much of the material in the volume has resulted from Professor Knoefel's own studies and has not hitherto been reported. Altogether, this is an excellent reference source for pharmacologists, clinicians, and, especially, radiologists.

CHAUNCEY D. LEAKE
Columbus, Ohio

Management of Hypertensive Diseases

JOSEPH C. EDWARDS, M.D., 1960. *St. Louis: C. V. Mosby. 439 pages. Illustrated. \$15.00.*

Dr. Edwards has compiled an excellent review of literature on hypertensive diseases in this volume. The bibliography is superb, although some subjects are more completely covered than others. Included in the book is a very good pharmacologic review of all drugs used in the treatment of hypertensive diseases.

The author favors the use of the more potent antihypertensive drugs, especially the blocking type, before trial of the milder antihypertensive drugs, such as Rauwolfia and diuretics. If large quantities of drugs, especially of the ganglionic blocking variety, are needed, it is our feeling that sympathectomy should be strongly considered. In this reviewer's opinion, sympathectomy is definitely indicated in patients with malignant hyper-

tension who have good kidney function. While the survival rate of patients treated with drugs fared well when compared with that of the surgically treated patients, it must be taken into consideration that most physicians do not concentrate on treating hypertension to the degree mentioned by the author in this volume. According to other groups, such as the Smithwick group, the survival rate among the medically treated, as a whole, is much less when compared with that of patients treated surgically.

Management of Hypertensive Diseases is written in a very clear and logical form. While some subjects are more thoroughly treated than others, this well-illustrated volume would be an excellent reference book for all physicians, particularly those interested in the field of hypertensive cardiovascular diseases. However, we must remember that, while this book clearly presents the problems of hypertension and its treatment at the present time, the rapid development of new drugs and methods of study indicate that this is merely the first chapter in a long series. Many new editions will be needed before the final chapter on the treatment of hypertensive diseases is written.

DERA KINSEY, M.D.
Boston, Massachusetts

Texts in Pharmacology

Pharmacology and Therapeutics

ARTHUR GROLLMAN, M.D., fourth edition, 1960. *Philadelphia: Lea & Febiger. 1,079 pages. Illustrated. \$12.50.*

Medical Pharmacology: Principles and Concepts

ANDRES GOTH, 1961. *St. Louis: C. V. Mosby. 551 pages. \$11.00.*

Pharmacology, The Nature, Action and Use of Drugs

HARRY BECKMAN, second edition, 1961. *Philadelphia: W.B. Saunders. 805 pages. \$15.00.*

These 3 pharmacology texts are excellent, which is to say that they are conventional, stereotyped, and clearly presented for helpful reference. None of them offers much in the way of basic principles beyond brief routine considerations of drug sources; absorption, fate, and excretion of drugs; structure-action relations; dose-effect relations; and details on drug administration. This introductory material could well stand expansion.

The balance of the volumes summarizes actions and uses of drugs classified according to organs and systems. While this classification is time-honored, it is not currently satisfactory with the extension of pharmacologic knowledge into medical applications for the diagnosis of disease and the prevention of disease. While drugs are mostly used for the alleviation of the symptoms of disease, there is also increasing current interest in drug use for the promotion of optimum health.

The circumstances of organization are not important, however, since students and physicians will find these books well arranged for specific information. Current ideas are well discussed and well documented.

Pharmacology is being increasingly applied to many practical matters other than medicine. These include the other health professions, as well as agriculture, pest control, warfare, and sociology. In these matters, there are factors with which physicians must be concerned, since so many of these growing applications of pharmacologic knowledge involve potential toxic hazards, with which

(Continued on page 14A)

BOOK REVIEWS

(Continued from page 13A)

physicians must be acquainted, not only for prevention, if possible, but also for management, should they occur.

These, and other texts in pharmacology, offer busy medical men the best sort of review of the rapid current advance of pharmacologic information. This advance is now so great that the textbooks go out of date within a few years and need repeated revision.

CHAUNCEY D. LEAKE
Columbus, Ohio

Anesthesia and the Law

CARL ERWIN WASMUTH, M.D., 1961. Springfield, Ill.: Charles C Thomas. 105 pages. Illustrated. \$5.00.

This new, timely, small book, which is indexed, printed on good paper, and easy to read presents an important phase of the practice of medicine which physicians will not read about unless they are compelled to. The author makes the point which is most important now, that no longer will the law treat an anesthetist on the basis that he need be no better than the other physicians in his community. This book serves a most useful purpose. Samples of forms for consent of anesthesia and operation are shown, and the sound principles to be observed in avoiding medicolegal difficulties, in the case of both the anesthesiologist and the nurse-anesthetist, are made clear.

JOHN S. LUNDY, M.D.
Chicago

Diabetes, with a Chapter on Hypoglycemia

ROBERT H. WILLIAMS, M.D., editor, 1960. New York: Paul B. Hoeber. 793 pages. Illustrated. \$20.00.

This volume might be more appropriately termed "A Symposium on Diabetes," since it consists of a series of reviews by 54 highly competent investigators in this multifaceted disease, many of whom draw freely from their personal experiences and research. The latter approach, posed in textbook form, may sometimes mislead the less experienced clinician seeking an answer to therapy of problem patients. For example, the flat statement is made that "in modern diabetes therapy there are only two indications for the use of unmodified insulins." These are "to accelerate and intensify the action of depot insulins . . ." and "to adjust insulin dosage rapidly to suddenly increased demands during acute complications in diabetes" (page 474). Such a statement is entirely too dogmatic, conveying the impression of unanimous agreement on this precept among qualified therapists. Recently, Wildberger and Ricketts (J.A.M.A. 172:655, 1960) and, previously, this reviewer (J.A.M.A. 142:168, 1950) both reported a total of 16 diabetic subjects whose long-range control improved significantly when multiple injections of unmodified insulin were substituted for various combinations of modified insulins. Rather than considering this routine "virtually intolerable," as stated in Williams' text, none of these patients insisted on resuming his previous insulin program.

Utilized as a reference source, this book has many excellent features but cannot supplant Joslin's time-honored text, which is far more comprehensive in its treatment of intimate problems of everyday clinical practice. Published a year later than Joslin's text, the timely subject of oral hypoglycemic agents is much more adequately covered in Williams' text. It is recommended for the practitioner's book shelf with the foregoing reservations.

E. A. HAUNZ, M.D.
Grand Forks

Child Development and Child Psychiatry

CHARLES SHAGASS, M.D., and BENJAMIN PASAMANICK, M.D., editors, 1960. Washington, D.C.: American Psychiatric Association. 225 pages. \$2.00.

This issue of the psychiatric research reports, a tribute to Dr. Arnold Gesell in his eightieth year, has a moving introduction by Dr. Leo Kanner. There are a few articles which will interest pediatricians and general practitioners who are alert in child and adolescent development.

Knobloch and Pasamanick present an interesting evaluation of the consistency and predictive values of the 40-weeks' Gesell developmental schedule. This will reinforce the use of the test.

McCandless' presentation of the rate of development, body build, and personality will interest the physician who observes the adolescent male with more than the casual eye.

Papers on micropsia, maternal behavior and personality development, data from the Berkeley growth study, conforming and deviating behavior, and the problem of guilt all could be discussed profitably in groups.

All the presentations are followed by prepared discussions and interesting bibliographies.

HERSCHEL J. KAUFMAN, M.D.
Minneapolis

NEW BOOKS RECEIVED

Books and publications received will be listed here periodically, and such mention must be regarded as sufficient return for the courtesy of the sender. Books of special interest to our readers will be reviewed as space permits.

Adrenergic Mechanisms. G. E. W. WOLSTENHOLME and MAEVE O'CONNOR, editors, 1960. Boston: Little, Brown & Co. 632 pages. Illustrated. \$12.50.

Annual Report of the Board of Regents of the Smithsonian Institution. Washington: United States Government Printing Office, 1960. 686 pages. Illustrated.

Chemical Osteosynthesis in Orthopaedic Surgery. MICHAEL P. MANDARINO, M.D., 1960. Springfield, Ill.: Charles C Thomas. 63 pages. Illustrated. \$4.50.

Emotional Maturity. LEON J. SAUL, M.D., 1960. Philadelphia: J. B. Lippincott. 372 pages. Illustrated. \$6.50.

Basic Medical-Surgical Nursing. MILDRED A. MASON, R.N., 1959. New York: Macmillan Co. 513 pages. Illustrated. \$4.95.

Chemistry of Thyroid Disease. ROSALIND PITT-RIVERS, Ph.D., and JAMSHED R. TATA, M. SC., 1960. Springfield, Ill.: Charles C Thomas. 68 pages. Illustrated. \$4.50.

Clinical Management of Behavior Disorders in Children. HARRY BAKWIN, M.D., and RUTH MORRIS BAKWIN, M.D., 1960. Philadelphia: W. B. Saunders. 590 pages. Illustrated. \$10.50.

Congenital Malformations. G. E. W. WOLSTENHOLME, M. A., and CECILIA M. O'CONNOR, editors, 1960. Boston: Little, Brown & Co. 292 pages. Illustrated. \$9.00.

(Continued on page 16A)



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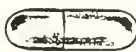
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BOOK REVIEWS

(Continued from page 14A)

Differentialdiagnose innerer Krankheiten. PROF. DR. ROBERT HEGGLIN, 1960. Germany: Georg Thieme Verlag. 868 pages. Illustrated. \$18.95.

Dietary Proteins in Health and Disease. JAMES B. ALLISON, PH.D., and WILLIAM H. FITZPATRICK, PH.D., 1960. Springfield, Ill.: Charles C Thomas. 71 pages. Illustrated. \$4.50.

Electron Microscopy of the Cardiovascular System. BRUNO KISCH, M.D., 1960. Springfield, Ill.: Charles C Thomas. 164 pages. Illustrated. \$7.50.

Embolic Dispersoids in Health and Disease. GUS SCHREIBER, M.D., 1960. Springfield, Ill.: Charles C Thomas. 71 pages. Illustrated. \$5.50.

English for the Foreign Physician. JOSE MURILO MARTINS, M.D., 1960. Springfield, Ill.: Charles C Thomas. 92 pages. Illustrated. \$5.75.

Haemopoiesis: Cell Production and Its Regulation. G. E. W. WOLSTENHOLME, M.A., and MAEVE O'CONNOR, editors, 1960. Boston: Little, Brown & Co. 466 pages. Illustrated. \$11.00.

Human Pituitary Hormones. G. E. W. WOLSTENHOLME, M.A., and CECILIA M. O'CONNOR, editors, 1960. Boston: Little, Brown & Co. 321 pages. Illustrated. \$9.50.

Instructional Course Lectures. FRED C. REYNOLDS, M.D., editor, 1959. St. Louis: C. V. Mosby Co. 323 pages. Illustrated. \$16.00.

An Introduction to Public Health. HARRY S. MUSTARD, M.D., and ERNEST L. STEBBINS, M.D., 1960. New York: Macmillan Co. 313 pages. Illustrated. \$5.00.

Medical Care of the Adolescent. J. ROSWELL GALLAGHER, M.D., 1960. New York: Appleton-Century-Crofts. 356 pages. Illustrated. \$10.00.

Medicine as an Art and a Science. A. E. CLARK-KENNEDY, M.D., and C. W. BARTLEY, M.D., 1960. Philadelphia: J. B. Lippincott. 408 pages. \$6.25.

Mental Drugs: Chemistry's Challenge to Psychoanalysis. O. A. BATTISTA, 1960. Philadelphia: Chilton Co. 134 pages. \$3.95.

Personal Health Record Book. WILLIAM B. SCHOENING, 1960. Minneapolis: T. S. Denison & Co. 128 pages. \$2.25.

Preventive Medicine. HERMAN E. HILLEBOE, M.D., and GRANVILLE W. LARIMORE, M.D., 1959. Philadelphia: W. B. Saunders. 702 pages. Illustrated. \$12.00.

Regulation of the Inorganic Ion Content of Cells. G. E. W. WOLSTENHOLME, M.A., and CECILIA M. O'CONNOR, editors, 1960. Boston: Little, Brown & Co. 93 pages. Illustrated. \$2.50.

A Manual of Bandaging, Strapping, and Splinting. AUGUSTUS THORNDIKE, M.D., 1959. Philadelphia: Lea & Febiger. 153 pages. Illustrated. \$2.75.

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA,
NORTH DAKOTA, SOUTH DAKOTA, AND MONTANA

FOREWORD

THIS ISSUE of *The Journal-Lancet* is planned to highlight the contributions of anatomy to the field of medicine. The date of publication coincides with the seventy-fifth annual meeting of the American Association of Anatomists which is being held in Minneapolis March 20 through 23, 1962.

The first article in this issue is a history of the Department of Anatomy at the University of Minnesota, prepared by Dr. J. Arthur Myers. Because of his long association with the University and his intimate knowledge of the department, Dr. Myers is well qualified to write such an account. He also consulted with Dr. E. T. Bell, who had close association with this department. This paper emphasizes the great contributions made by Minnesota anatomists in the past but does not cite research contributions of the present staff because we are too close in time to evaluate these; this is being left to the future.

In gathering material for this special issue, it has been interesting to note the impressive careers of those who received their Ph.D. degrees in anatomy from Minnesota; these are tabulated on page 140. Unfortunately, because of space limitations, the data about those receiving the Master's degree could not be included, but many of these persons have also attained distinction in medicine and related scientific fields.

The other papers in this issue deal with some of the contributions that anatomists, in general, have made and are making to the fields of medicine, surgery, hematology, endocrinology, growth and development, radiology, and neurology. Most of these special articles were written by individuals who received their Ph.D. degrees from the Department of Anatomy at Minnesota. The authors of these are Professors Thomas Dougherty, Donald Duncan, Oliver P. Jones, Charles R. Noback, Gordon Scott, and Raymond Truex. Dr. Leo Rigler was formerly professor of radiology at the University of Minnesota, and Dr. Stewart Thomson, professor of public health at the University of Minnesota, began his career as an anatomist.

As guest editor, I am deeply indebted to these men and wish to express my personal appreciation to each of them for the time and effort which have gone into preparing his contribution.

In the final article of this issue, entitled "The Fourth Dimension of Anatomy," I have tried to correct a common misconception that anatomists are concerned only with "bones and cadavers." New developments in instrumentation and technique during the past several decades have carried anatomy into a new era of research which could not have been foreseen a generation ago.

ARNOLD LAZAROW, *Guest Editor*

HISTORICAL SKETCH

University of Minnesota Department of Anatomy

J. ARTHUR MYERS, M.D.

Minneapolis

PART I

Beginning to 1912

IN 1881, the University of Minnesota took the initial step toward creating a Department of Medicine, a Constitutional privilege which had been granted under the State Constitution of 1853.

ORGANIZATION

On June 29, 1882, Dr. Charles N. Hewitt proposed to the Board of Regents the organization of a department of medicine and the Board appointed a committee to present a plan of organization. The chief duty of the first faculty, consisting of 5 members, was to serve as an examining board to determine who should be licensed to practice medicine in Minnesota. The first meeting was held on April 23, 1883.

In 1887, a petition was presented to the Board of Regents of the University of Minnesota to establish a high-grade teaching department of medicine and to the Legislature to provide for its means. On February 28, 1888, the faculties of 2 private medical schools—the St. Paul Medical College and the Minnesota Hospital College—appeared before the Board of Regents in support of the University School, with the offer to surrender their charters and with the tender of their property for the temporary use of the State. A month later, the Minnesota College of Homeopathy surrendered its charter.

The first teaching faculty consisted of 29 members who had their first meeting on June 8, 1888, with Dr. P. H. Millard as dean.

For approximately twenty years, a dean, to whom each faculty member was responsible, presided over the Department of Medicine. However, in 1909, the faculty was organized into 10 units known as departments. A head or chief was appointed for each department.

In October 1888, the first student entrance examinations were held. The fees were \$35 per

year for residents of the state and \$60 for non-residents. Dissecting material was extra and scarce. The course of study consisted of three years of six months each. However, two years later, this was extended to eight months each year and, in 1891, to nine months.

Standards were increased from time to time and, in 1902, one year of University premedical work was required for admission to the medical department. In 1908, this was increased to two years.

The building of the Minnesota Hospital College was leased and became the temporary residence of the new department of the University (figure 1). This building, located on the corner of Sixth Street and Ninth Avenue in south Minneapolis, was a considerable distance from the University campus. An outpatient department was established in a building at 1908 Washington Avenue (Seven Corners) which was about midway between the leased medical building and the University campus.

On October 4, 1892, Sir William Osler of Johns Hopkins University delivered the dedication address, "Teacher and Student," for the first medical building on the campus. The new building, known as Medical Hall (later Millard Hall), was



Fig. 1. First building occupied by University of Minnesota Medical Department from 1888 to 1893 at Sixth Street and Ninth Avenue South, Minneapolis. Anatomy was taught in this building.

J. ARTHUR MYERS is professor emeritus of public health and medicine, University of Minnesota.



Fig. 2. First building of the Medical Department on University of Minnesota campus. This was named Medical Hall (later known as Millard Hall) and was occupied in the fall of 1893. Gross anatomy was taught in this building.

occupied in 1893 (figure 2). Gross anatomy was taught in the new Medical Hall; histology, pathology, pharmacology, and bacteriology were housed in another new but smaller structure, the Chemistry Building, constructed the same year (figure 3). In 1895-96, the Laboratory of Medical Sciences was added to the medical buildings to which such subjects as histology, pathology, and physiology were removed.

In 1908, a New Institute of Pathology and State Board of Health Building (later named Westbrook Hall) was completed. In 1905, a bequest to be devoted to the building of the Elliot Memorial Hospital came from the estate of Dr. and Mrs. A. F. Elliot. This building was completed in 1911.

In 1909, the Legislature appropriated funds for two new buildings, which were ready for occupancy in 1912; one was known as Millard Hall, the other, as the Institute of Anatomy (figure 4).

PRESIDENTS OF THE UNIVERSITY

William Watts Folwell became president in 1869. He was instrumental in having Dr. C. N. Hewitt appointed professor of public health in 1874. Two years before Folwell's retirement in 1884, the Board of Regents appointed him as one of three to plan the organization of a medical department. In this post, he later named 5 physicians to serve as a nonteaching faculty. The

school with the teaching faculty, organized in 1888, was under the administration of *Cyrus Northrup*, who served as president from 1884 to 1911, the year when Elliot Memorial Hospital was built and Millard Hall and the Institute of Anatomy were under construction. In 1911, George E. Vincent became president.

DEANS OF THE DEPARTMENT OF MEDICINE

When the medical faculty was organized, the school was known as the Department of Medicine. All persons in the various subjects included in the school were directly responsible to *Dean P. H. Millard* until he died in 1897. He was succeeded by *Dr. H. Parks Ritchie* who



Fig. 3. This structure was erected the same year as Medical Hall and was known as the Medical Chemistry Building. It housed chemistry, bacteriology, histology, pathology, and pharmacology.

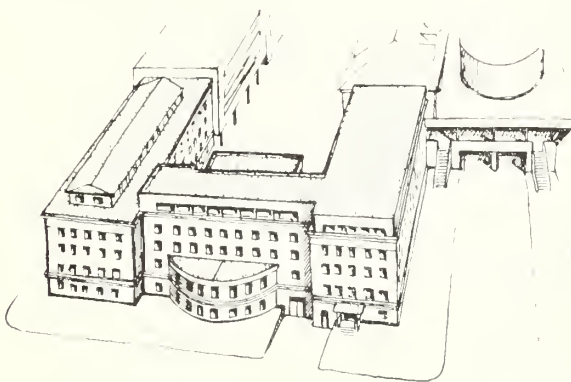


Fig. 4. East view of the Basic Science Quadrangle of the College of Medical Sciences. The center unit and the wing to the left constitute the original building constructed in 1912 and now named Jackson Hall. The wing to the right is the new addition completed in 1961 and known as the E. T. Bell-Peter J. Brekhus Laboratories. The departments of anatomy and pathology are housed in Jackson Hall and the Bell-Brekhus Laboratories are shared by the departments of anatomy and pathology and the School of Dentistry. The domed structure in the background to the right is the Mayo Memorial Auditorium.

served until 1906. *Frank E. Wesbrook* was then Dean until 1913. It was during his administration that the school was divided into departments, with each department under a head.

It was during Dean Wesbrook's administration that the Institute of Pathology and the State Board of Health Building, Elliot Hospital, Millard Hall, and Institute of Anatomy were constructed.

FACULTY MEMBERS IN ANATOMY

Among the 29 members of the teaching faculty of 1888 was *Dr. George A. Hendricks*, professor of anatomy (figure 5). A former student at the University of Michigan School of Medicine, in 1877, he became assistant demonstrator in anatomy and, in 1881, curator of the medical museum. From 1882 to 1888, he was instructor in anatomy and, from 1884 to 1889, he served as editor of the *Physician and Surgeon*, the journal founded in 1879 with Dr. Victor C. Vaughn as managing editor. The associate editors were members of the medical faculty. This journal ceased publication in 1915.

At Minnesota, beginning in 1888, he was better known as a teacher than as a practitioner, although he was an expert operator and a skillful surgical diagnostician. He was a born teacher and was universally beloved by his students. He occupied the chair of anatomy until September

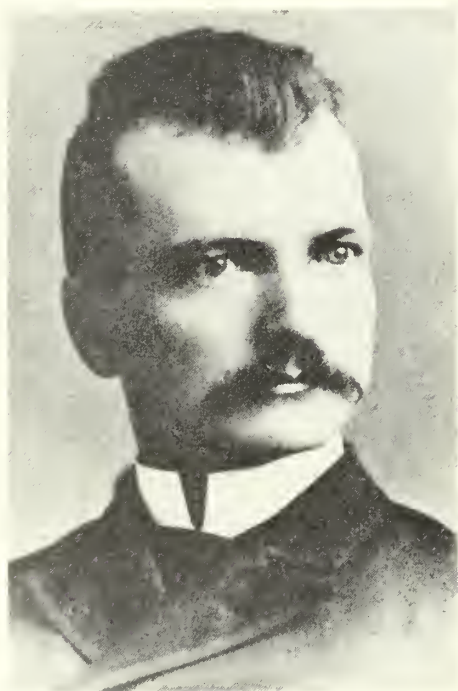


Fig. 5. George A. Hendricks (1891), professor in charge of anatomy, 1888 to 1899.

1899, when he died from "acute Bright's disease" at the age of 49. Dr. R. O. Beard later wrote of him, "He was of the most genial nature, of faithful service and of scholarly attainments."

Dr. Arthur F. Ritchie also served as professor of anatomy in 1888. He had graduated in medicine at McGill University in 1876 and was licensed to practice medicine in Minnesota in 1884. Apparently he taught anatomy here only one year. He later practiced medicine in Duluth through 1906 and died at Mount Clemens, Michigan, in April 1907 at the age of 52.

During the first few years, *Dr. E. C. Spencer* was professor of surgical anatomy, *Burnside Foster* was demonstrator, and *J. Clark Stewart* was professor of histology, bacteriology, and pathology.

From 1891 to 1894, *Dr. Charles L. Green* was professor of surgical and applied anatomy and *Dr. Frank Burton* was demonstrator.

In 1891, *Thomas G. Lee* became instructor in histology, bacteriology, urinalysis, and embryology. Born in the state of New York in 1860, he received his B.S. and M.D. degrees from the University of Pennsylvania in 1886. During the last two years there, he was student assistant in histology and embryology. He was also awarded the B.S. degree at Harvard University. Following graduation from Pennsylvania, he went to Yale, where for five years he was lecturer in histology and embryology and director of laboratories. He also taught these subjects for one year at Radcliffe College.

After one year at Minnesota he was promoted to a professorship in histology, embryology, bacteriology, and clinical microscopy. In 1909, when the Medical School was departmentalized, Dr. Lee became the first chief of the Department of Anatomy (figure 6). On beginning his work as an instructor, he brought into being the laboratory of histology and embryology and devoted his time to teaching and research.

In a history of medical education in Minnesota presented by Dr. R. O. Beard in 1908 is the following:

The historian notes, in the minutes of 1892-3 that Dr. Thomas G. Lee preferred a request to be assigned the subject of embryology and modestly asked for one didactic hour a week in histology and bacteriology combined, during the entire session. The Faculty evidently felt the necessity for curbing the rising ambition of this and other related chairs, and Professor J. Clark Stewart rose to faculty fame in the putting of a motion which limited histology to 64 laboratory hours; embryology to 10 lectures; bacteriology to 12 didactic hours; pathology to 32 hours; and anatomy, chemistry, and materia medica were limited to 128 hours each.

For many years, Dr. Lee served as secretary

of the medical faculty. As librarian (1909 to 1913), he devoted much time to the foundation and development of the medical library. Soon after graduation, he had studied in Europe and later visited the various laboratories in Europe and America while developing plans for a special building for the Department of Anatomy. Dr. Lee devoted a tremendous amount of time to this project. When it was completed in 1912, it was named the Institute of Anatomy and was regarded as one of the finest structures of its kind in this country. He held membership in many scientific organizations in the fields of biology and medicine. In 1910, he attended the International Congress of Anatomists at Brussels and the International Zoological Congress at Graz.

Dr. Lee was active in the investigation of mammalian embryology and made several contributions on the early development, implantation, and placentation of rodents. Between 1892 and 1918 he published 13 scientific articles.

With the reorganization of the School of Medicine in 1913, Dr. Lee became professor of Comparative Anatomy. In 1929 he reached retirement age and became professor emeritus after thirty-eight years devoted to teaching anatomy at the University. After retirement he lived at Babson Park, Florida. He died on September 1, 1932, from injuries sustained in an automobile accident.

Charles A. Erdmann was graduated from the University of Wisconsin in 1887 and from the University of Minnesota School of Medicine in 1893. He served three years as a student assistant in anatomy and, upon graduation, became demonstrator in anatomy. In 1898, he became an assistant professor and, in 1900, professor of anatomy. From 1909 to 1913, he was professor of gross and applied anatomy; after 1913, he was associate professor of applied anatomy.

Dr. Erdmann devoted his life almost exclusively to teaching. When the Department of Anatomy was reorganized in 1913 and Dr. Jackson promoted an extensive research program, Dr. Erdmann requested that he be assigned a heavy teaching load so other staff members could devote more time to research.

He was an exceedingly popular teacher as he made the students enjoy the dissection course which, in many places, was considered heavy and dull. He was intensely interested in each student and was pleased and proud of every success and honor each may have attained. He kept on his desk Louis Burton Woodward's poem, "Because I would be young in soul and mind"

For a number of years he worked with the state and national associations of morticians in developing educational standards for embalmers and funeral directors. He served continuously at the University except for a brief period of study in Vienna in 1900. It was said that he never missed a day of work on the campus. Dr. Erdmann remained in the department and carried a heavy teaching load for forty-three years. In fact, he taught some sons of his earlier students in the School of Medicine. In a newspaper interview at the time of his retirement in 1936, he said that medical students had changed but little in the past forty-three years. "The type of man the profession attracts is always the same, a good student, not necessarily a brilliant one, but a person imbued with the ideals of service to mankind. It has always been the same."

He developed general arteriosclerosis and died from bronchopneumonia in February 1941, at the age of 74.

In 1898 *W. H. Nickerson* was appointed instructor in histology at the University of Minnesota. He was born in Massachusetts in 1864 and received the B.S. degree from Harvard University in 1890 and his D.Sc. degree in 1894. From 1891 to 1894, he was assistant in zoology at Harvard. In 1894-95, he was professor ad interim of biology at the University of Colorado; in 1895-



Fig. 6. Thomas G. Lee, professor in charge of anatomy, 1900 to 1908 and head of Department of Anatomy, 1909, 1913.

96, he was instructor in mammalian anatomy and histology at Northwestern University, and in 1896-97, he studied in Europe, spending most of his time in Germany. At Minnesota, he was promoted to an assistant professorship in 1899 and completed the medical course in 1905. From 1906 to 1912, he was assistant professor of anatomy. Thereafter, he practiced medicine in several North Dakota and Minnesota towns, the last in Farihaunt. He died in Redford, Massachusetts, at the age of 81.

Dr. W. H. Nickerson's wife, *Margaret L.*, was appointed instructor in histology in 1898. A graduate of Smith College, she received her M.A. at Radcliffe in 1897, took the M.D. degree at Minnesota in 1904, and taught histology until 1908. She died in 1942.

John B. Johnston was born in Ohio, October 3, 1868. In 1893, he received the degree of bachelor of philosophy from the University of Michigan and remained there the next six years as assistant and instructor in anatomy. He was granted his Ph.D. in 1899. From Michigan, he went to the University of West Virginia as associate professor of zoology and head of the department. There he was promptly advanced to a professorship. During the year 1904-05, he studied at Naples Zoological Station and at Freiberg. He was appointed assistant professor of anatomy of the nervous system at the University of Minnesota in 1907, advanced to associate professor of comparative neurology in 1908, and to professor in 1909. The year before coming to Minnesota he had published his famous book entitled "The Nervous System of Vertebrates," which was extensively followed by subsequent neurologists.

"Beginning with 1899," A. T. Rasmussen of neuroanatomy fame said, "then followed fifteen years during which he produced an astonishing amount of work chiefly on the morphology and evolution of the forebrain and of the mechanism of correlation of the vertebrate nervous system."

Dr. Johnston became dean of the College of Science, Literature, and Arts in 1914. He also retained his professorship in comparative neurology and conducted research in this field as late as 1922. By 1923, he had published 45 scientific papers and a "Guide to Embryology." As Rasmussen said, "Dr. Johnston's scientific career was motivated by a consistent program of research which was formulated at the beginning and carried through with great vigor and fidelity to the original purpose."

He was an active member of the editorial board of the *Journal of Comparative Neurology* from 1908 to 1933 and of the *Ergebnisse und*

Fortschritte der Zoologie from 1907 on. For these journals he performed exacting and time-consuming duties, promptly, faithfully, and judiciously.

When he became dean of the College of Science, Literature, and the Arts, he became aware of important educational problems that needed investigation, and, about 1923, turned his entire attention to these problems. He published 37 educational papers, 6 being chapters in books and 3, additional books of his own.

"As a teacher he is remembered as a modest personality with clear and simple diction, marshalling masses of detail into vivid and orderly scientific concepts made possible by a gifted insight and a conviction of purpose," wrote one of his colleagues. He held membership in numerous national organizations. He was a member of Sigma Xi, Phi Beta Kappa, and Gamma Alpha. In recognition of his achievements both as a neuroanatomist and as an administrator, he was granted the honorary degree of Doctor of Science by the University of Michigan in 1933.

Dr. Johnston attained the retirement age in 1937, after which he traveled in the Orient and later in South America. He died on November 18, 1939, at Palo Alto, California.

In 1910, *E. T. Bell* came to Minnesota as assistant professor of anatomy. He was born in Missouri in 1880. He earned his B.S. degree at the University of Missouri in 1901 and his M.D. degree in 1903. He served in the Department of Anatomy at Missouri as assistant in 1902-03, instructor from 1903 to 1907, and assistant professor from 1907 to 1910. These years of work were under the directorship of C. M. Jackson, head of the Department of Anatomy. He came to the University of Minnesota in 1910 as assistant professor of anatomy and transferred to pathology in 1911. In these years he helped to attract Dr. R. E. Scammon and Dr. C. M. Jackson to the University of Minnesota.

Dr. Bell became head of the Department of Pathology in 1920, continuing to retirement in 1949. From the time of his arrival, he wielded great influence in the development of the Medical School. His interest in the Department of Anatomy never abated. In collaboration with Dr. Scammon and Dr. Jackson, he was an outstanding leader in the development of a strong medical research program.

Richard E. Scammon was appointed assistant professor of anatomy in 1912, when he was 29 years old. He and Dr. Bell were roommates, so they were influential in having C. M. Jackson tendered an important position when the Medical School was reorganized in 1913. Dr. Scam-

mon had an excellent record, having received his B.A. from the University of Kansas in 1904, his M.A. from Kansas in 1906, and his Ph.D. from the newly established Division of Medical Sciences at Harvard in 1909.

Indeed, he was the first person to take a doctorate in medical sciences in this country. His thesis, on the embryology of the dogfish, was of such size and importance that it was printed in series. He was teaching fellow at Harvard in 1907-09 and instructor in anatomy from 1909 to 1910. In 1911-12, he was associate professor of anatomy at the University of Kansas.

On the campus of the University of Minnesota, it was frequently said that Dr. Scammon was the best teacher and best scholar, not only of the School of Medicine but of all the schools. In writing about him in 1952, Harry Wilmer said, "He mastered many subjects: anatomy, embryology, the history of science, logic, mathematics, the populations of the world, history, philosophy, and his particular love, the growth of man."

Allen Boyden wrote that Scammon had a universal mind. He was an authority on mathematics, economics (he devised the university retirement system), history (ecclesiastical or otherwise), church architecture (he took yearly pilgrimages to England) and all branches of anatomy. He had a photographic memory. He was an omnivorous reader and considered it a day wasted unless he had read one book in the twenty-four hours. He became the leading world authority on physical growth.

In 1930, Dr. Scammon became a professor in anatomy and dean of the Division of Biological Sciences, University of Chicago, but remained there only one year because Minnesotans urged him to return. In 1931, he became the first dean of medical sciences, a position created especially for him, then, in 1935, he moved into another new position as distinguished service professor in the Graduate School. On retirement in 1949 he moved to Branson, Missouri, and died on September 12, 1952, on his small farm, "Few Acres," where he had taken great delight in growing flowers.

All Scammon's friends and colleagues believed that those who lured him into administrative work had made a great mistake. Concerning this, Wilmer said, "It is no wonder that being a dean was failure to him. He was prone to describe deaning as being an honest gambler, a man who sat at the gaming table with a green shade over his eyes and turned up card after card without caring what it was. Scammon as a dean was an anachronism that could not endure."

Scammon devoted most of his research in anatomy to studies on human growth. At the time of his death, a tremendous volume of material had been accumulated and he had outlined several volumes of material for publication which had been planned through the Commonwealth Fund.

Unfortunately, no manuscript was ready for publication at the time of his death. However, through the Graduate School of the University of Minnesota, an arrangement was made whereby Edith Boyd, who had worked for a number of years with Scammon, would proceed to complete the various volumes. Mrs. Scammon and the Commonwealth Fund requested that the series be called "The Major Patterns of Human Growth" and that they be published under Dr. Boyd's name, with a statement that they were based upon Dr. Scammon's unfinished work. The first volume, entitled "Origins of the Study of Human Growth," is now in press, and the next two are in preparation. The tentative titles of the next 4 volumes are as follows: "Iconometric-graphic Analysis," "Quantitative and Graphic Analysis," "Scammon's Annotated and Classified Bibliographies," and "Individual and Age Changes in External Body Form."

From 1888 to 1912, many instructors, University scholars, assistants, and demonstrators participated in teaching. There were far too many to even list their names in the space here available but they are to be found in the University Archives; suffice it to say that among them were such prominent names as *Herbert W. Jones*, *A. E. Booth*, and *J. E. Hynes*.

PART II 1913 to 1962

PRESIDENTS OF THE UNIVERSITY

From 1911 to 1917, George E. Vincent served as president and it was he who reorganized the Medical School. He was succeeded by Marion LeRoy Burton from 1917 to 1920. Lotus Delta Coffman, who served from 1920 to 1938, was responsible for procuring and promoting the Continuation Study Center where special courses in anatomy have been presented. Guy Stanton Ford, longtime dean of the Graduate School, was president from 1938 to 1941; he was followed by Walter Castella Coffey, who served until 1945. His successor, James Lewis Morrill, worked unceasingly with Dean Harold S. Diehl in the promotion of the extensive Medical School building program. He was followed in 1960 by Dr. Meredith O. Wilson who, like each of the preceding presidents, is giving a full measure of support

to teaching and research in all departments of the Medical School.

MEDICAL SCHOOL DEANS

From 1913 to 1936, Elias P. Lyon was dean of the School of Medicine. However, from 1931 to 1935, Dr. Richard E. Scammon served as dean of medical sciences.

From 1935 to 1958, Harold S. Diehl was dean of medical sciences. During his administration, a tremendous building program was instituted, including the Mayo Memorial Building. Since 1958, Dr. Robert Howard has made superior contributions as dean of the College of Medical Sciences. Each dean has played a tremendously important role in supporting and developing the Department of Anatomy.

MEDICAL PHOTOGRAPHY AND ILLUSTRATION

No historical sketch of the Department of Anatomy would be complete without consideration of the Department of Medical Photography and Illustration.

Photography. The need for first class medical photography in the operation of the School of Medicine was early recognized. As a high school student in 1906, Henry Morris began working afternoons in the pathology laboratory which was headed by Dr. Frank Westbrook and located in the University Free Dispensary Building at 1908 Washington Avenue South, Minneapolis. In 1907, Henry accepted the proposal of Dr. Westbrook, then dean of the Medical Department, to go to Rochester, New York, and study at the Eastman Kodak Company for a year and thus become a full-fledged photographer. When this course was over Henry requested permission to do additional work at Rockefeller Center in New York. To this, Dean Westbrook replied, "Stay as long as necessary but come back a photographer."

The Photographic Department was set up on the third floor of the new Institute of Pathology in the State Board of Health Building now known as Westbrook Hall. Morris's studio was moved to the Institute of Anatomy when that building was completed in 1912 and remained there until 1957 when it was moved to the Mayo Memorial Medical Center. Although he did work for the entire School of Medicine, he was looked upon as belonging to the Department of Anatomy where he had his office for forty-five years.

Soon after the move to the Institute of Anatomy, that department became very prolific in preparation of research manuscripts. The Department of Anatomy, as well as the entire Medical School, took great pride in his expert work

which brought him many honors. In 1920, he received the Blue Ribbon and Certificate of Achievement from the Royal Photographic Society; in 1946, he was given a fellowship in the Biological Photographic Association of which he was a charter member, and, in 1956, he was honored by the Eastman Kodak Company on his fiftieth anniversary as a photographer. Henry Morris contributed mightily to the success of nearly all persons who have worked in the Department of Anatomy since 1909.

Illustration. This work began when the Department of Anatomy employed a part-time artist with a studio in a brown frame house on Washington Avenue at the approximate site of today's Murphy Hall. From time to time, work was done for other departments of the School of Medicine. In 1908, the illustrating department was moved to the Dentistry Building and, in 1912, to the second floor of the Institute of Anatomy, where it became known as the Medical Art Shop. For several years the work was directed by Miss Katherine Whitney. When she resigned in 1917, she was succeeded by Miss Jean Hirsch, who was highly qualified by reason of training and experience. She produced literally thousands of illustrations for the faculty of the Department of Anatomy. In 1926 her Art Shop became an independent department, serving all departments of the School of Medicine. The department remained in the Institute of Anatomy, now Jackson Hall, until 1957, when it was combined with the photographic department as the Department of Medical Art and Photography and moved to the Mayo Medical Center.

THE GRADUATE SCHOOL

The first dean of the Graduate School, H. T. Eddy, who served from 1905 to 1912, was succeeded by Guy Stanton Ford, who held the post until 1938. Early in Dean Ford's administration, the Department of Anatomy became especially active in providing graduate students. In fact, Dr. C. M. Jackson, for so long head of the Department of Anatomy, was in such favor with the Graduate School that, on several occasions, he served as acting dean of that school in Dean Ford's absence.

When Dean Ford resigned in 1938, he was succeeded by R. N. Chapman, who died after about four months of service. Theodore C. Blegen was then appointed Dean in 1940. For the next eighteen years a large number of candidates from the Department of Anatomy received graduate degrees under his direction. When Dean Blegen reached retirement age he was succeeded by Bryce Crawford, Jr.

Soon after his arrival in 1911 as third president of the University, George E. Vincent reorganized the School of Medicine.

Clarence Martin Jackson, dean of the School of Medicine and head of the Department of Anatomy at the University of Missouri was offered the deanship of the School of Medicine at Minnesota. Jackson had received both his M.S. and M.D. degrees from the University of Missouri; during 1899-1900, he had served as instructor in anatomy; for the next two years, he was assistant professor; and, in 1902, he was appointed professor and head of the department. He spent 1903-04 in Leipzig and Berlin. In 1909, he was made dean of the Medical School at the University of Missouri.

Jackson was such an unusual teacher, administrator, and research worker that he became favorably known by anatomists throughout the country. When President Vincent decided to reorganize the Medical School of the University of Minnesota, he aspired to have as dean the most capable young man available. Jackson possessed all of the desirable qualifications. However, when he told President Vincent that he preferred not to be engaged in full-time administrative work, he was invited to become professor and head of the Department of Anatomy, a position which he accepted at a lower salary than that of the deanship, since he desired to devote the remainder of his life to teaching and research (figure 7).

Jackson organized the department in a unique manner, retaining all persons who were on the staff at the time of his appointment. Those who wished to teach were assigned heavy teaching schedules, while those who desired to do investigative work were provided with every facility he could give them.

Dr. Jackson was continuously engaged in his own research projects, as well as directing those conducted by other members of his staff. He published more than 100 articles; edited Morris's "Human Anatomy" from the fifth through the ninth edition; prepared a monograph, "Effects of Inanition upon Growth and Structure," and wrote chapters and sections for books by other authors. A methodical man, he periodically bound reprints of his published articles together with those by the members of his staff. A series of 16 such volumes appeared under the title "Contributions from the Department of Anatomy, University of Minnesota."

Dr. Jackson was a regular attendant at the annual meetings of the American Association of

Anatomists, serving as president from 1922 to 1924. For many years, he was a member of the Advisory Board of the Wistar Institute of Anatomy, and, for a long period, he was chairman of the American Committee on Anatomical Nomenclature and an American member of the International Commission. He attended the International Medical Congress in Madrid in 1903 and the International Congress of Anatomy which met in Amsterdam in 1930 and in Milan in 1936. In 1923, the University of Missouri bestowed upon him its highest honor, the honorary degree of Doctor of Laws. He received distinguished service awards from Sigma Xi in 1940 and from the Minnesota State Medical Association in 1941.

He was president of the Minnesota State Board of Examiners in Basic Sciences for more than a decade and a starred member of the American Men of Science. At the University of Minnesota, he served as chairman of the medical graduate committee from 1915 to 1941. He also served as acting dean of the Graduate School from 1917 to 1918 and again in 1925. In 1923 and 1924, he was chairman of the Medical Division of the National Research Council in Washington, D. C. For many years he was associate editor of the *American Journal of Anatomy*. In 1933, the Phi Beta Pi medical fraternity of which he had long been a member established a Clarence Martin Jackson lectureship, which



Fig. 7. Clarence M. Jackson, professor and head of Department of Anatomy, 1913 to 1941.

continues to be an important annual event on the campus.

His voice and manner inspired confidence, and he was the personification of kindness. He was a prodigious worker and could be found in his office throughout the day and often in the evening.

At the time of his retirement it was said, "His ability as a teacher, investigator and administrator, his fine contributions to the literature, his unquestioned character, his honesty, truthfulness and trustworthiness in every respect, together with the absence of any manifestation of jealousy or selfishness, have won for him a place among America's truly great physicians of all time." It was often said that Dr. Jackson was more responsible than anyone else for improving teaching and developing a research program in the School of Medicine. His contributions were so many, the regard for him so high, and his memory so cherished that, in 1954, on recommendation of the Faculty, the Board of Regents changed the name of Institute of Anatomy to Jackson Hall.

Promptly after his appointment as head of the Department of Anatomy, Dr. Jackson sought promising young teachers. He continued employing instructors and student assistants, many of whom later became widely known, including *Chester A. Stewart* of pediatric fame; *J. C. McKinlay*, who became head of the Department of Neurology and Psychiatry; and *William Peyton*, who developed and long directed the Division of Neurosurgery.

Hal Downey. Jackson's good judgment was manifested when he appointed Hal Downey to his staff. Dr. Downey's father was a mathematician who served as dean of the Academic College of the University of Minnesota. As a boy, Hal studied for six years in Hannover, Germany. He was graduated from the University of Minnesota in 1903 and was granted a master's degree in Zoology in 1904. From 1903 to 1929, he was with the Department of Zoology, having advanced rapidly to a professorship. That year, on the invitation of Dr. Jackson, he became professor of anatomy.

From 1913 to 1959, except during the two World Wars, he served as the American editor of *Folia Haematologica*, published in Leipzig. In this connection, the first page of the *Minnesota Alumni Weekly* for January 27, 1913, carried his portrait and an article which pointed out that he had recently done some remarkably good work on the structure of the blood cells and their relationship to each other and the lymph nodes. Downey's work, said the article, was the best

that had been done in this country, bringing to the Department of Animal Biology great prestige in the field of blood investigation. In 1938, he edited the "Handbook of Haematology," which had 34 contributors and 3,136 pages in 4 volumes. No comparable work in hematology had previously been projected in any language.

Downey received the outstanding achievement award of the University of Minnesota in 1951 and the distinguished service award of Sigma Xi in 1957. In the citation for the first award, it was said:

You have given this University fame in hematology. . . . Although your world-renowned paper on infectious mononucleosis describing the cells which now bear your name is known for its correlation of critical morphologic detail with clinical conditions, many other prophetic contributions on reticular and lymphatic tissues as well as on all types of blood cells are the foundations for much active research. . . . Your control of the world's bibliography of hematology . . . your editorship of the *Folia Haematologica* and your own Handbook of Haematology further affirm your scholarly desire to integrate ideas.

C. A. McKinlay, who participated in the pioneer studies of infectious mononucleosis with Downey wrote:

The first contact of the writer with Dr. Downey was in consideration of a case seen in 1921 in which acute leukemia was the primary clinical impression due in part to hemorrhagic tendency, marked adenopathy, and lymphocytosis. The benign hematological features, however, were recognized and recorded by Dr. Downey as the cells were all mature lymphocytes.

Interest was stirred in the problems presented by this case, which represented a new entity to clinical observers and which was confirmed as such hematologically by Dr. Downey in a series of 9 cases reported jointly in 1923. His colored plate and description of type I, II, and III cells were classical for finer hematologic features and became in the succeeding years standard laboratory criteria for confirmation of clinical diagnosis of infectious mononucleosis.

Although infectious mononucleosis has been recognized as a widespread disease of young people affecting practically all organ systems and although the positive heterophil test has become the common laboratory confirmation of diagnosis, the cytology as described by Dr. Downey remains at least for the hematologist and those who can appreciate morphology, the best criterion for recognition of the disease.

Dr. Downey will always be remembered as a patient and diligent seeker of truth, a true scientist who gave generously of his skills and attainments to students and physicians who sought his scholarly aid.

E. Dorothy Sundberg who succeeded Dr. Downey following his retirement wrote as follows:

The world will correctly say that he was a scholar, but it is doubtful that the world can ever find in Dr. Downey's publications the essence of the man. Perhaps that essence was gentleness, personal humility, intellectuality, humor, and a certain horror of poor histologic technique—"histologic garbage"—and slipshod scientific con-

tributions of any type. His alert and sparkling brown eyes almost always betrayed a quiet amusement with, as well as a sincere concern for, the activities of cells or people. He never forgot what either did. His students were his colleagues, not his underlings; he worked for them, though they did not know it. . . .

After reaching retirement age in 1946, he lectured for two years at the Mayo Clinic and Mayo Foundation. As professor emeritus, he remained in the department as an active investigator and beloved colleague whose wisdom and intellectual acumen could ill be spent until the Christmas holidays of 1959, when he died at the age of 82.

Another demonstration of Dr. Jackson's ability in choosing staff members was the selection of *Andrew T. Rasmussen*. He was born in Utah in 1883 and, in 1909, received the B.A. degree from Brigham Young University, where, two years later, he was made head of the Department of Biology. From 1913 to 1916, he was instructor and graduate student in the departments of physiology and anatomy at Cornell University, receiving his Ph.D. in 1916. Dr. Sutherland Simpson, chairman of this committee in the graduate school, and Dr. A. T. Kerr, a member of the committee, considered Dr. Rasmussen the best student they had taught. In the fall of 1916, he became an instructor in anatomy at the University of Minnesota and, by 1925, he had been promoted to full professor.

Rasmussen prepared excellent teaching material. Before his retirement, his "Laboratory Directions in Neuroanatomy" appeared in several editions, his "Outlines of Neuroanatomy" had gone through the eighth printing of the third edition, and his "Principal Nervous Pathways" had gone through four editions. His books, which were originally prepared only for his own classes, became texts in many medical schools. These, together with more than 80 other publications and his unique demonstration collection of more than 500 specimens, greatly facilitated the teaching of neuroanatomy in this country.

Rasmussen was also one of the most popular members of the Graduate School faculty. Concerning that work, Theodore Blegen, dean of the Graduate School, said, "I cannot praise too highly the constructive contributions of Dr. Andrew T. Rasmussen to graduate studies and the Graduate School through his many years of service, but the truth is that they do not need praise. They speak for themselves."

On Dr. Rasmussen's retirement in 1952, Dr. Boyden, then head of the department, said:

Faculty and students alike will miss Dr. A. T. Rasmussen after thirty-six years of distinguished service in the Department of Anatomy. He became known as an au-

thority on the anatomy of the pituitary gland and as one of the leading neuroanatomists in the country.

Dr. Henry W. Woltman of the Mayo Clinic and Mayo Foundation for Medical Education and Research, University of Minnesota Graduate School, said:

Among Dr. Rasmussen's warmest admirers are the graduate students of the Mayo Foundation who had the privilege of studying neuroanatomy under him. Clinical neurology and neurosurgery especially, and certain fields of medical practice such as ophthalmology, otology, psychiatry and psychology owe their stability to the sciences that underlie them and perhaps the most basic of these is neuroanatomy.

Dr. Rasmussen is one of the greatest teachers of neuroanatomy of our time. He built up probably the most outstanding collection of gross and histologic neuroanatomic specimens in existence.

Rasmussen taught neuroanatomy to more than 4,000 regular medical students and approximately 200 postgraduate students.

On February 1, 1954, he was appointed visiting professor at the University of Southern California, where he made his usual brain dissections, stained microscopic slides, and drew large colored charts for the class. At the close of the class in June he donated many boxes of his own microscopic slides, charts, and colored drawings to augment the teaching aids of the Anatomy Department.

In September 1954, at the invitation of Dr. Horace Magoun, professor of anatomy of the University of California at Los Angeles, Dr. Rasmussen visited the research facilities in the Department of Investigative Medicine of that school. He decided he would like to make a complete series of brain dissections like those used in the teaching of neurology and have them embedded in clear plastic for permanent use. He selected the most perfect brains and used extra care in their dissection. Robert Oller, who had perfected the plastic process, did the embedding. The group of more than 70 such specimens has been designated "The Rasmussen Collection."

After retirement from the University of Minnesota he received the distinguished service award from Brigham Young University in 1953. In January 1954, he was called back to the University of Minnesota to deliver the J. B. Johnson lecture. In February 1955, he accepted from McGill University the offer of a three-month visiting professorship at the Montreal Neurological Institute.

That spring he gave a number of notable lectures—the annual Cajal lecture at the meeting of the American Association of Anatomists, the annual neurological lecture at the Montreal Neu-

rological Institute, the William Gibson lecture at the University of Buffalo, and a lecture to the anatomy students at the University of Michigan.

Upon returning to California he continued making brain dissections. In early September 1955, he began working feverishly to go to Yale University where he was to be made visiting professor in the Medical School and give an advanced course in neurology. However, before completing preparations, he died suddenly from a heart condition on October 15, 1955.

Following his death his friends contributed to a memorial fund which provided for a special Rasmussen collection on neurology in the library of the Department of Anatomy.

Shirley Miller began working with the Department of Anatomy as a teaching fellow in 1920. He was born in Rockwell, Iowa, and was graduated from the Northwestern University Academy. In 1903, he received the B.S. degree from South Dakota State College at Brookings and the next year he earned the M.S. degree in zoology, bacteriology, and pathology at the University of Minnesota. From 1908 to 1911 he studied zoology and anatomy in Germany. On returning to the United States, he became professor of vertebrate zoology and public health at South Dakota State College. During 1916-17 he was engaged in a research project at the University of Chicago, then continued at State College until 1920. After receiving his Ph.D. in anatomy in 1922, he continued teaching in the department of anatomy. Because of a serious eye condition which made it impossible to continue using the microscope, he was confined to teaching gross anatomy. In 1927 he was promoted to assistant professor. After reaching retirement age in 1946, he taught general biology and zoology at Augsburg College, Macalester College, and Hamline University for a total of five years. Since 1947, he has been abstracter for articles in German, French, and Italian for *Medica Acta*. During the same period he has been on the Council of AAAS and, from 1947 to 1950, was secretary of Minnesota Academy of Science.

Edward Allen Boyden. When R. E. Scammon transferred to the University of Chicago in 1931, Dr. Jackson appointed Edward Allen Boyden, professor of anatomy at the University of Minnesota, to take charge of the lecture course in embryology and to assist in the teaching of anatomy. Boyden had received his B.S. degree, magna cum laude, from Harvard in 1908 and his M.S. degree in 1911. After a year at the Institute of Anatomy in Freiberg, Germany, he returned to Harvard as a teaching fellow, receiving

his Ph.D. in medical sciences in 1916. He was then appointed instructor in anatomy at Harvard and advanced to assistant professor three years later.

In 1926 he was made associate professor and later professor of anatomy at the University of Illinois. In 1929 he was called to the University of Alabama to reorganize their anatomy department. As soon as this was done, he accepted the position at the University of Minnesota where he soon restored laboratory work in embryology and prepared a "Laboratory Atlas of a 13-mm. Pig Embryo" which was published in 1933 by the Wistar Institute. His famous work on the gallbladder, begun in 1922, is described by Dr. Leo Rigler in this issue of *The Journal-Lancet*.

While at Harvard, Boyden examined 10,000 mammalian livers at the abattoirs in the vicinity of Boston. There he met and conversed with "kosher cutters" from a local synagogue who informed him that the anomalies for which he was searching had been described in the Babylonian Talmud and its codifications. After coming to Minnesota, he contacted S. I. Levine, senior rabbi of Minneapolis, and interested him in translating the anatomic portions of the sixteenth century codification, the Shulchan 'Aruch. For eight years, Rabbi Levine and Dr. Boyden devoted one night every week to the study of this source material. The University of Minnesota Press published the translation in 1940 and the entire edition was promptly sold.

Early in his career at Minnesota, Boyden began publishing reports of unusual cases found in the dissecting room, among them the double ductus choledochus. In Dr. Jackson's collection, he found in a 10-mm. human embryo the first case of unilateral agenesis of the kidney, caught in the act of disappearing so the etiology was revealed.

When in 1940 C. M. Jackson was placed on half-time appointment because of failing health, Dr. Boyden was made acting head. That year he took over the course in gross anatomy which he had previously conducted during summer sessions.

Upon Dr. Jackson's retirement in 1941, the Department of Anatomy was placed in charge of a committee of 3 full professors with Dr. Boyden as chairman. He became head of the Department in 1949 (figure 8).

Dr. Boyden's work on bronchopulmonary segments began in 1945, when Owen H. Wangenstein, chief of surgery at University of Minnesota, asked him to appear before a staff conference to discuss the segmental anatomy of the lungs. Although Brock's fundamental work had

appeared, no adequate "maps" of the lungs had been included in the literature to show the relation of the bronchi, arteries, and veins in the different lobes, so Boyden hurried to make some preliminary dissections prior to appearing before this conference. His first paper on the subject was published in December 1943 in *Surgery*. Thereafter, for nine years, a series of original articles appeared analyzing the variations in the segments. The value of this work is also presented in more detail by Dr. Rigler in this issue of *The Journal-Lancet*.

As antimicrobial drugs became available, as anesthesiology improved, as liberal use of blood was employed, and as surgical techniques advanced, the chest began to yield its secrets to the surgeon. Allen Boyden's contributions to segmental anatomy of the lungs, which taught the surgeon which diseased segments could be removed without sacrificing an entire lobe or a lung, was significant. His book, entitled "Segmental Anatomy of the Lungs. A Study of the Patterns of the Segmental Bronchi and Related Pulmonary Vessels," which appeared in February 1955, is the first of its kind. It is packed with important new information which is indispensable to students, teachers, and clinicians.

He has published more than 130 papers in scientific and medical journals, 25 of them since retiring from Minnesota. In 1928, he became managing editor of the *Anatomical Record* and edited the next 62 volumes. Concerning this work, Charles H. Denforth recently said:

Few not on his board, and those only to a degree, could have been aware of the effort that went into shaping these volumes into the monument that they are. The critical reading of each paper, the pertinent questions, the helpful suggestions, the firm but sympathetic restraint on the overenthusiastic, the immature, and the ill-informed have borne real if intangible fruit, for here no less than in the classroom and the seminar, Dr. Boyden has been, as he continues to be, a potent influence in shaping the quality and the direction of American anatomy.

In 1954, Dr. Boyden reached retirement age, whereupon his friends contributed to a fund of the Minnesota Medical Foundation. This was invested in the seminar room of the Department of Anatomy, which Dr. Boyden had always considered to be the center of the life of the Department. Among other items a plaque is displayed in the room with the following inscription: "In honor of Edward Allen Boyden, professor and head of the Department of Anatomy, University of Minnesota." Another is a bookplate made from an original oil painting by Edward Brewer of St. Paul. Prints of this are

attached to the 275 volumes which Dr. Boyden gave to the Department of Anatomy.

Numerous honors have been bestowed upon him. In 1928, the University of Illinois awarded him the William Beaumont Prize, and, in 1937, the Southern Minnesota Medical Association presented him with its gold medal. The editorial board of the *Anatomical Record* and others interested in anatomy produced a Boyden birthday volume which included 4 numbers, January through April 1954. The first article, entitled "In Honor of Edward Allen Boyden," contains a detailed account of his life and work.

In 1955, he was appointed one of the delegates to the International Congress of Anatomists in Paris, having participated in the revision of the "Nomina Anatomica." In 1954, he received a citation from the Minnesota State Medical Association for his contributions to the surgery of the lung. In 1956-57, he served as president of the American Association of Anatomists. In 1960, he received the award for distinguished achievement given by *Modern Medicine* and, in 1961, was made honorary fellow of the American College of Chest Physicians.

As research professor at the University of Washington, he is devoting most of his time to studies on the postnatal growth of the lung and to his duties as American editor of *Acta Anatomica*.



Fig. 8. Edward Allen Boyden, professor of anatomy from 1931 to 1954 and head of the department from 1949 to 1954.

At Minnesota, he is remembered not only for his work on the biliary tract and the lung, but for his impact on the teaching of gross anatomy for the fourteen years in which he conducted that course. By his analysis of anatomic pattern in the lung, his use of surgical films, freshman clinics, his seminars with the Department of Surgery, and his selection of material which is clinically significant to the medical student, he aroused an enthusiasm for the subject which will long be remembered by his students.

His contributions have been so important that, wherever teaching and research are conducted in anatomy and wherever diagnostic and therapeutic work is done, particularly on the gall-bladder and the lungs, the name Edward Allen Boyden is known and will continue to be known through the generations.

Raymond F. Blount, who had worked in zoology at Yale University, became instructor in anatomy at Minnesota in 1931. He was born in LaGrange, Illinois, in 1900 and attended school in Phoenix, Arizona. He was granted B.S. and M.S. degrees by the University of Arizona in 1924 and 1926 and the Ph.D. by Yale University in 1931. While teaching zoology and anatomy at Yale, he was offered a position as instructor in anatomy at the University of Minnesota. Here he worked on transplantation experiments in salamanders and learned a good deal about how the oral portion of the hypophysis induces formation of the neural portion. In subsequent years, Blount joined Dr. Jackson in expanding the chapter on the digestive system in Jackson's tenth edition of "Morris' Anatomy," as well as providing new figures in the cardiac and other sections of the book in the eleventh edition. After Dr. Jackson retired, Blount became responsible with Dr. Lachman for the chapter on the digestive system. Blount was also responsible for organizing the course in anatomy for nurses. In 1942, he accepted a position as associate professor in anatomy, University of Texas. Since 1943, he has been professor of anatomy in that institution.

Edith Boyd was appointed associate professor of anatomy in 1934. A graduate of the School of Medicine of Johns Hopkins University, she had been a fellow in the Mayo Clinic in 1924, instructor in Pediatrics in 1925-26, and instructor in the Institute of Child Welfare in 1927.

At Minnesota, she was an excellent teacher. She worked mainly with Dr. Scammon and, in 1941, assembled their work under the title, "Outlines of Physical Growth and Development." This volume, which was issued by the Burgess Publishing Company, condensed many studies and made them readily available.

She resigned in 1941 and, for the next five years, was superintendent of the hospital at Whitefish, Montana. In 1946, she became assistant professor of physical growth, University of Colorado Medical School, then served as professor from 1952 to her retirement in 1959. She holds membership in many scientific and medical societies and has published a number of articles in addition to the 5 volumes on the major patterns of human growth which she is now editing.

Arthur Kirschbaum, who was born in New York City in 1910, received his B.S. degree from New York University in 1931. He then came to the University of Minnesota where he earned his M.S. in zoology in 1935, his Ph.D. in anatomy in 1936, and his M.D. degree in 1943. He was fellow and instructor in the Department of Anatomy at Yale from 1937 to 1941, when he returned to Minnesota to serve as assistant professor from 1942 to 1945 and as associate professor from 1945 to 1951. After three years as professor and chairman of the Department of Anatomy at the University of Illinois, he accepted a similar position at Baylor University and, in addition, served as chairman of anatomy in the University of Texas Dental Branch and consultant for cancer research at the Anderson Hospital.

Dr. Kirschbaum's research program dealt with neoplasms of the mammary gland, adrenal cortex, and ovary of inbred mice. His work on cancer began at Yale with a study of leukemia in mice; this interest continued throughout his lifetime.

Dr. Kirschbaum distinguished himself as a gifted and stimulating teacher, he held membership in numerous medical and scientific organizations, and he served on editorial boards of scientific publications. In addition, he was appointed consultant to the United States Public Health Service, and the American Cancer Society and was a member of the President's National Health Advisory Council.

Following Dr. Kirschbaum's sudden death in 1958 from coronary occlusion at the age of 48, Dr. Boyden said of him, "His untimely death was a great loss to basic medical science." Dr. R. A. Liebelt of Baylor had this to say: "Dr. Kirschbaum was an inspiring leader in all his fields of endeavor because of his sincerity, ability, recognition of the individual, endless energy, and the strength of his conviction."

Berry Campbell, who was born in St. Paul, Minnesota, in 1912, received his B.A. degree from the University of California (Los Angeles) in 1932, and his Ph.D. in anatomy from Johns Hopkins in 1935. He was a National Research Council fellow at Western Reserve from 1935

to 1937, served as assistant professor of anatomy at the University of Oklahoma from 1937 to 1942, became a fellow at Columbia from 1942 to 1943, then came to Minnesota as assistant professor of anatomy. He became associate professor in 1945 and professor in 1958. Dr. Campbell left Minnesota in 1958 to become professor of neurology at the College of Medical Evangelists in Los Angeles, now known as Loma Linda University. His research interests are neuroanatomy and neurophysiology.

W. Lane Williams was born in Rock Hill, South Carolina, in 1914. After graduation from Wofford College in 1935, he received his M.A. degree from Duke University in 1939 and his Ph.D. from Yale in 1941. He served as instructor of anatomy at the Rochester School of Medicine and Dentistry in 1941-1942 and at Yale in 1942-1943. He was assistant professor of anatomy, Louisiana State University, from 1943 to 1945, then became assistant professor at Minnesota in 1945 and associate professor in 1949. He left Minnesota in 1958 to become professor and chairman of anatomy at the University of Mississippi. Dr. Williams' research interests are histochemistry and experimental pathology.

Olof Larsell, long-time head of anatomy at the University of Oregon, came to Minnesota for a two-year period, following Dr. Rasmussen's retirement in 1952. Dr. Larsell, born in Sweden in 1886, was graduated with a B.S. degree from

Linfield College in Oregon in 1910. He received his M.S. and Ph.D. degrees from Northwestern University in 1914 and 1918, respectively. He served as instructor of zoology at Northwestern (1915 to 1918), assistant professor of anatomy at Wisconsin (1918 to 1920), associate professor of zoology, Northwestern (1920-1921), as professor and head of anatomy at the University of Oregon (1921-1952). In 1954, he reached the Minnesota retirement age and returned to Portland.

Professor Larsell is the author of "Anatomy of the Nervous System," a standard textbook of neuroanatomy, and wrote the section dealing with the nervous system in "Morris's Anatomy." His interest in medical history led to the publication of "The Doctor in Oregon." Dr. Larsell is a world authority on the anatomy of the cerebellum in man and other vertebrates. While at Minnesota, he had the opportunity to write his great monograph on the cerebellum, which is now in the process of being published by the University of Minnesota Press.

PRESENT STAFF

Arnold Lazarow became professor and head of the Department of Anatomy upon Dr. Boyden's retirement in 1954. Dr. Lazarow (figure 9) was born in Detroit, Michigan, in 1916, and received the following degrees from the University of Chicago: B.S., 1937; M.D., 1941; Ph.D., 1941. He interned at the Woodlawn Hospital in Chicago in 1942 and served as research associate at the University of Southern California in 1943. He was a senior instructor in anatomy at Western Reserve University from 1943 to 1946, assistant professor from 1946 to 1948, and associate professor from 1948 to 1954, at which time he came to Minnesota.

Dr. Lazarow holds memberships in 13 medical and scientific organizations including the American and the International Associations of Anatomists. His outstanding recognition among national and international workers and organizations is manifested by trusteeship of the Cleveland Diabetes Society, 1953-54; board of directors, Twin City Diabetes Association, 1954, and president 1955 and 1956; participant in International Diabetes Symposium in Leiden, 1952; Council of Histochemical Society, 1952-56; advisory council on Research on Pathogenesis of Cancer, American Cancer Society, 1956-58; consultant, study section—metabolism and nutrition, USPH Service 1957-61; Advisory Editor of *Cytochemistry*, Journal of the National Cancer Institute, 1950-52; Council of American Diabetes Association, 1956-62; study section, cell biology,



Fig. 9. Arnold Lazarow, professor and head of the Department of Anatomy, 1954-.

1960-61; National Advisory Council of the Institute for Arthritis and Metabolic Diseases, United States Public Health Service; Minnesota Medical Foundation, board of directors, 1957-61, president, 1960-62.

He has published more than 116 papers of which 68 are in the field of experimental diabetes, 22 microtechniques and 26 in cytochemistry. He has an unusually high rating as a teacher among the students and enjoys great respect and confidence of the faculty. Dr. Lazarow's research interests are in the fields of cytochemistry and experimental diabetes.

Lemen J. Wells, professor, came to the University of Minnesota in 1940. Dr. Wells was born at Mount Vernon, Illinois, in 1907. He received his B.E. degree from Southern Illinois State Teachers College in 1927, his M.S. degree from Northwestern University in 1928, and his Ph.D. degree from the University of Chicago in 1934. He served as instructor in anatomy at the University of Missouri from 1935 to 1937 and as assistant professor from 1937 to 1940. At the University of Minnesota, he was associate professor from 1940 to 1949, when he became full professor. Dr. Wells' research interests are in embryology and fetal endocrinology.

J. Francis Hartmann, professor, joined the department in 1945. Dr. Hartmann was born at Rochester, New York, in 1910 and received his B.A. from Holy Cross College in 1932 and his Ph.D. degree from Cornell in 1943. From 1943 to 1945, he was instructor in anatomy at Albany Medical College. Coming to Minnesota as an instructor in 1945, he became assistant professor in 1946, associate professor in 1951, and full professor in 1957. Dr. Hartmann's research interests concern electron microscopy and the nervous system.

Charles F. Morgan, professor, came to Minnesota in 1959. Dr. Morgan was born in Cherokee, Oklahoma, in 1911, and received his B.A. from the University of Wichita in 1933 and his Ph.D. from the University of Chicago in 1942. He served as instructor in pharmacology at Georgetown University (1942-1943), assistant professor (1943-1946), and associate professor (1946-1947). He served as professor and director of the department of physiology at Georgetown from 1947 to 1958. He joined the University of Minnesota staff as professor in 1959. His current research is in the fields of experimental endocrinology and radioautography.

R. Dorothy Sundberg, professor of anatomy (hematology), was one of Dr. Downey's Ph.D. students. Dr. Sundberg was born in Chicago in

1915 and attended the University of Chicago, Wayne State University, and the University of Minnesota, where she received her B.S. degree in 1937, her M.A. in 1939, her Ph.D. in 1943, and an M.D. in 1953. She served as instructor in anatomy at Minnesota from 1943 to 1946, as assistant professor from 1946 to 1953, and associate professor from 1953 to 1960, when she became full professor. She became a diplomate of the American Board of Pathology (Hematology) in 1960. Dr. Sundberg has also served as hematologist, University of Minnesota Hospital laboratories, since 1940. Her principal area of research is experimental hematology.

Anna-Mary Carpenter, associate professor of anatomy, came to Minnesota in 1954. Dr. Carpenter was born in Ambridge, Pennsylvania. She received her B.A. degree from Geneva College in 1936 and her M.S. and Ph.D. degrees from the University of Pittsburgh in 1937 and 1940, respectively. She attended Western Reserve School of Medicine from 1953 to 1954 and completed requirements for her M.D. degree at the University of Minnesota in 1958. Dr. Carpenter served as chairman in the Department of Biology at Moravian and Keystone colleges from 1941 to 1944; as research associate in the Department of Pathology and Children's Hospital, University of Pittsburgh Medical School, from 1945 to 1953; as instructor of anatomy at Minnesota from 1954 to 1957; and as assistant professor until 1959, when she became associate professor. Her research interests are histochemistry, experimental diabetes, and mycology.

William J. L. Felts, associate professor of anatomy, joined the department in 1955. Born at Saginaw, Michigan, in 1924, he received his A.B., M.A., and Ph.D. degrees from the University of Michigan in 1948, 1951, and 1952, respectively. He served as instructor in anatomy at Indiana University during 1951-1952 and at Tulane University during 1952-1955. At Minnesota, Dr. Felts served as assistant professor from 1955 to 1960, when he became an associate professor. His present research interests are bone biology and transplantation.

Carl B. Heggstad, assistant professor, joined the anatomy staff at the University of Minnesota in 1958. Dr. Heggstad was born in Starbuck, Minnesota, in 1930. From the University of Minnesota he received his B.A. in 1952, his M.D. in 1957, and his Ph.D. in 1960. He was an intern in pediatrics at the University of Minnesota hospitals during 1957-1958. After serving as instructor in anatomy from 1958 to 1960, he became assistant professor in 1960. His research

is in fetal endocrinology and placental physiology.

Morris Smithberg, assistant professor, was born in Brooklyn, New York, in 1924 and received his A.B. from Brooklyn College in 1948 and his Ph.D. from the University of Rochester in 1953. He served as research fellow and staff member at the R. B. Jackson Memorial Laboratory from 1952 to 1957 and as assistant professor at the University of Florida from 1957 to 1960, at which time he came to Minnesota. Dr. Smithberg's research studies are in experimental embryology and reproductive physiology.

Mary Jane Buckman, instructor of anatomy, was appointed in 1959. Dr. Buckman was born at Little Falls, Minnesota, in 1917. She has received the following degrees from the University of Minnesota: B.S. in 1940, M.S. in 1958, Ph.D. in 1959. She served as medical technologist at St. Andrews Hospital, Minneapolis; at St. Gabriels Hospital, Little Falls; and at the University of Minnesota Hospitals from 1940 to 1954. Dr. Buckman's current research is in experimental hematology.

SUMMARY

In 1888, anatomy was a subject taught in the Department of Medicine, which was housed in a single building some distance from the campus. In 1909 it assumed departmental status, and in 1912 it moved into a building of its own. This original building has been extensively remodeled during the past few years and a new addition, providing research facilities, was completed in 1961 (figure 4).

In 1888, bodies for dissection were hard to obtain; today, each group of 4 medical students is furnished with a body for study. Many of these bodies come to the University through specific bequests.

In 1888, there was no provision for research; today, the Department of Anatomy has excellent facilities and equipment. These include: radioisotope, histochemistry, and cytochemistry laboratories; 3 electron microscopes; and a variety of specialized instruments.

In 1888, there were 2 part-time professors of anatomy; 1 part-time professor of histology, bacteriology, and pathology; and 1 part-time demonstrator of anatomy. From that beginning, the evolution of teaching and research has progressed until today the anatomy staff includes 61 full-time and a number of part-time members.

The Minnesota legislative appropriation provides for a regular staff of 5 professors, 2 associate professors, 3 assistant professors, 1 instructor, and several part-time instructors. Outside fund-granting agencies, primarily the United States Public Health Service, support 7 full-time research associates and fellows who participate in projects being carried out in the department. There are 26 trainee-graduate students working for advanced degrees. There are 24 full-time civil service and technical personnel and many part-time employees on the technical staff, most of whom are supported by outside research grants.

The University of Minnesota can be proud of its tradition in anatomy extending over seventy-four years. This state can be proud to claim these great men in Anatomy—Jackson, Seammon, Rasmussen, Downey, Boyden, and Larsell—and the many students whom they have trained and who went on to distinguished careers.

Among the many persons who have aided in assembling the data contained in this manuscript, the following have been especially helpful: Mrs. Maxine B. Clapp, principal librarian, University of Minnesota Archives; Dr. Robert Rosenthal, chairman, Historical Committee, Minnesota State Medical Association; and Eleanor Hayes, Correspondent Control Unit, Physicians Record Section, American Medical Association.

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Some British Teachers of Anatomy and Their American Pupils

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BEFORE 1765, a young man in the American colonies who wished to become a physician had two alternatives: (1) he could apprentice himself for several years to a physician in practice or (2) he could go abroad and study at some European medical school which granted a medical degree or take courses at proprietary schools established by some of the widely known physicians in foreign cities such as London.

The first medical school in the North American colonies was not established until 1765. The first session of the new school, affiliated with the College of Philadelphia, which later became the University of Pennsylvania, was held November 18, 1765. King's College School in New York, now the College of Physicians and Surgeons of Columbia University, was founded in 1767. Harvard did not open its medical school until 1783.

Thus, for a long period of years, many young men of the Colonies crossed the Atlantic for medical instruction. This was expensive, but the advantages of the European education appealed to those who could afford it and wanted the best training available. A large number of the apprentices to local physicians continued their studies in Europe.

Among these students was John Morgan, who studied with John Redman of Philadelphia from 1750 to 1756 before going to London. Benjamin Rush was also an apprentice of John Redman after his graduation from the College of New Jersey (now Princeton) but later went to Edinburgh and London. Even after medical schools were begun in this country, young men who wished to study medicine served apprenticeships and took courses from physicians who taught special classes.

American anatomy owes a deep debt of gratitude to the European teachers of anatomy who taught the young men from the New World. The

latter, in turn, became the teachers by whom instruction in anatomy was begun in this country.

SOME BRITISH TEACHERS

Several of the European teachers are worthy of particular remembrance. William and John Hunter, two Scots who established schools in London, were teachers of marked ability and, like magnets, drew many pupils. William Cheselden, even before the Hunters, had made a name for himself because of his teaching ability. Alexander Monro primus and his son, Alexander Monro secundus, attracted large numbers of students to Edinburgh.

In fact, Edinburgh became the new medical Mecca. Packard¹ has written that the medical degree from Edinburgh "was held in much higher esteem than that obtainable anywhere else in the United Kingdom, ranking with that of Leyden, from which university its methods of teaching and practice were largely derived." John Moultrie² of Charleston, South Carolina, received his medical degree from Edinburgh in 1749, the first of many men from the American colonies to graduate in medicine abroad. From 1726 to 1799, there were 195 persons from the West Indies and the North American continent who received Edinburgh degrees in medicine. All but 1 of 7 men prominent in the early history of the first medical school in this country had received training at Edinburgh.³

From men such as William Cheselden, Alexander Monro primus, William Hunter, John Hunter, and Alexander Monro secundus, the content and teaching methods of anatomy were transmitted to young Americans, who, in their turn, taught the subject to their countrymen.

William Cheselden. William Cheselden was without a doubt the outstanding anatomist and surgeon of England during the first half of the eighteenth century.⁴ A native of Somerby, later also the birthplace of Tennyson, he probably had his first training under Mr. Wilkes, who en-

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joyed considerable reputation as a surgeon of Leicester. As a student, he was greatly influenced by 2 of his teachers in London, James Ferne, surgeon-in-chief to St. Thomas's Hospital, and William Cowper, a widely known anatomist whose work, *Anatomy of Human Bodies*, appeared in 1698 and contained excellent plates made by Govert Bidloo.

Cheselden began to teach anatomy in 1710. In 1713, he published his *Anatomy of the Human Body*. This book was appropriately dedicated to Dr. William Mead as an expression of appreciation for Mead's lectures in anatomy and his help in encouraging Cheselden to write the book.

Mead, the physician mentioned by Samuel Johnson as living "more in the broad sunshine of life than almost any other man," was the second owner of the famous gold-headed cane of British medical history. The book exerted a tremendous influence, for it passed through 13 editions. Cheselden kept clearly in mind the needs of surgeons and said in his preface:

In describing the parts, I have pretty much neglected the Minutiae in Anatomy; nor have I been very particular about those things which cannot be understood without being seen, and being seen need little description; but have endeavoured to be more explicit about those which are of greatest use in Philosophy, Physic and Surgery; and I could wish the dividing and distinguishing of parts were usually done with more regard to these valuable ends.⁵

Cheselden became full surgeon to St. Thomas's Hospital in 1719 and held that position for nineteen years. As both a teacher of anatomy and a surgeon, his influence was felt widely.

Alexander Monro, primus, secundus, and tertius. Alexander Monro primus was appointed professor of anatomy in the University of Edinburgh ("the Town's College") on January 29, 1720. His father, John Monro (1670-1740), had seen to it that his son was well prepared for his career. After completing the arts course at Edinburgh and showing an inclination to study medicine, Alexander was sent to London to study under Cheselden.

According to Struthers,⁶ "it was in London, under Cheselden, that Monro learned anatomy, and how to teach it." Working together, Cheselden and Monro formed a friendship that lasted all their lives. Monro went on for further study in Paris and Leyden, where he became one of the favorite pupils of Boerhaave.

Alexander Monro was elected professor of anatomy in the University of Edinburgh at the age of 22. His first class had an enrollment of 57 students. Word of his excellent training and

ability spread, and each year the number of students increased. Struthers, in describing his course, says:

Monro's course extended from October to May, and embraced surgery as well as anatomy. His lectures were illustrated by dissections of the human body, and also, for comparison, of the bodies of quadrupeds, birds, and fishes. After giving the anatomy of each part, he treated of its diseases, especially of those parts requiring operations. He showed the operations on the dead body, and the various bandages and apparatus; and concluded the course with some lectures on physiology. He continued to give such a course uninterruptedly for thirty-eight years. He did not read his lectures. Even in giving the history of anatomy, with which he began his course, he spoke without the assistance of notes, except for the names and dates.⁶

Monro resigned from his professorship in 1758 at the age of 60, and his son, Alexander Monro secundus, began his duties as professor of anatomy in the winter of 1759. He had, after receiving his Edinburgh degree, spent two and one-half years, mainly in the study of anatomy, in London, Paris, and Berlin. He attended the lectures of William Hunter, just as Hunter had attended the lectures of his father. He spent time on the Continent with Albinus and Meckel.

Monro secundus, like his father, had large classes and did not lecture from notes. In fact, it has been told that, in order to have a complete set of his lectures, he purchased the notes taken by one of his pupils. He continued to lecture until the opening of the course in the fall of 1808. Among his contributions to anatomic knowledge were his studies on lymphatics and on the nervous system. The foramen connecting the lateral and third ventricles of the brain bears the name of Monro secundus.

Alexander Monro tertius (1773-1859) began his connection with the teaching of anatomy while his father was still professor of anatomy. He was, for ten years, a joint professor with his father and then continued as professor for thirty-eight years. The high standards of his grandfather and father were not maintained by Monro tertius. He even read his grandfather's lectures to his classes.

Thus, from 1720 until 1846, the chair of anatomy was occupied by 3 generations of the Monro family. Monro primus and tertius each taught thirty-eight years; Monro secundus taught fifty years. Their service to the teaching of anatomy covered one hundred twenty-six years. Monro secundus calculated that, during the seventy years from 1720 to 1790, his father and he taught 12,800 students. A document that contained this information was placed by Monro secundus in a bottle and deposited beneath the foundation

stone of the anatomic theater of the University, which was erected in 1790.⁶

The Hunters. There is a monument to William and John Hunter in the town of East Kilbride, Scotland, which is not far from Glasgow. Besides their names and dates, the inscription includes the following sentences:

They were born at Long Calderwood and died in London after attaining the highest eminence in the Sciences of Medicine and Surgery. Their names will be held in reverent remembrance by a grateful posterity to all generations.

American anatomy does well to remember the Hunters, for these two Scots were teachers of many of our nation's early physicians and teachers in our medical schools. The Hunterian influence was felt not only in Great Britain but in the New World. One of the centers of study with which their names are associated, the Great Windmill Street School of London, was a training center for teachers of anatomy for many years.

Although, today, more is remembered by most persons about John Hunter, it must be recalled that it was the elder brother, William, who trained and educated his youngest brother. Sir Benjamin Brodie, in the Hunterian Oration for 1837, spoke of John Hunter's debt to his older brother and said, regarding William: "It was as his pupil that John Hunter pursued his earliest studies in his profession: and it was under the influence of his example that he learned to cultivate as a science what was before little more than a practical art and trade."⁷

William Hunter (1718-1783) had been fortunate in the selection of the men with whom he studied. After his classical education at Glasgow University (his father had intended him for the ministry and he had prepared himself accordingly), William Hunter served an apprenticeship with William Cullen (1710-1790) at Hamilton. Cullen was later to become one of the University of Edinburgh's renowned teachers and a frequently consulted physician of "Auld Reekie."

Hunter also attended the lectures of Monro primus in Edinburgh.⁸ On his arrival in London in 1741, he came under the influence of another Scot, William Smellie (1697-1763), who was an anatomist and an accoucheur of no mean reputation. He began his studies in anatomy in London under Frank Nicholls (1699-1778), who was considered an outstanding teacher.⁹ Hunter lived in London at the home of James Douglas (1675-1742), an anatomist and obstetrician, who took deep interest in the career of this young man. Douglas had come to London from West Calder, Scotland.

Hunter also studied at St. George's Hospital under James Wilkie (d. 1750), then the senior surgeon-in-ordinary; he also spent a winter in Paris and there learned the French method of dissection. This was the method wherein each pupil was provided with an entire cadaver. The lecturer inspected the student's dissections.

William Hunter began his first course of lectures in anatomy on October 13, 1746. According to family tradition, as related by Miss Agnes Baillie, his niece, these classes were held in Covent Garden. The advertisement of the lectures in the *London Evening Post* for September 16, 1746, said that there would be an opportunity "of learning the Art of Dissecting during the whole winter season in the same manner as at Paris."¹⁰

During subsequent years, William Hunter taught his classes at various places, such as at the Little Piazza, the Great Piazza, the Chelsea China Warehouse in Piccadilly, and Litchfield Street. From 1756 until 1768, he lived at his house in Jermyn Street, where he saw patients but did not have rooms for lectures and dissections. It was with Great Windmill Street, however, that Hunter's name is especially associated.

Great Windmill Street School opened its doors on October 1, 1767. Hunter not only taught there but moved his residence to the new school. There he continued to live and teach until his death on March 30, 1783. Great Windmill Street School not only had good facilities for lectures and dissections but had a museum for the material Hunter had been collecting for years.¹¹

William Hunter had been fortunate in the selection of his teachers. He was equally fortunate in the choice of the assistants who taught with him. Even before he moved to Great Windmill Street, he had been assisted by his brother John and also William Hewson (1739-1774). In fact, the latter, when he arrived in London, had resided at Hunter's house in Great Piazza with John Hunter while attending William Hunter's lectures.

Hewson later became an assistant to William Hunter and subsequently a partner. The first course of lectures at Great Windmill Street referred to "Dr. Hunter's and Mr. Hewson's course of anatomical lectures."¹² A few years later, these men had a disagreement and the partnership was dissolved. Benjamin Franklin, then a resident of London, acted as mediator in the Hunter-Hewson difficulties and arranged the terms between the two on August 23, 1771.¹²

William Cruikshank (1745-1800) assisted Hunter from 1771 to late in 1774, when he became a partner. Cruikshank was a special friend of

Samuel Johnson, took care of him in his last illness, and was remembered in his will.

John Sheldon (1752-1808) gave lectures at Great Windmill Street School under Hunter and later, like Hewson, set up his own school of anatomy. It has often been said that Sheldon was the first Englishman to make an ascent in a balloon.

William Hunter was an enthusiastic teacher, and his enthusiasm was contagious. A teacher's influence, he wrote, "extends itself to the whole nation and descends to posterity."¹³ His pupils found his lectures full of interest. He used numerous illustrations from his fund of experiences. It was said that Hunter could make the dry details of descriptive anatomy come alive for his listeners. Like Alexander Monro primus, whose lectures he had attended in Edinburgh, William Hunter began his course with an account of the history of anatomy. Before he lectured on specific anatomy, he gave a general discussion concerning the parts of the body. His course concluded with lectures on the anatomy of the female reproductive tract and the problems associated with obstetrics.

As a teacher sincerely interested in his students' profiting from his courses, William Hunter's *Introductory Lectures*¹³ contain several items which he discussed when the courses opened. Some of these were:

1. He urged attendance at all his lectures and demonstrations, lest the pupil lose the continuity of the subject under study.

2. He stressed the value of demonstrations on the cadaver by the instructor preceding the student's own dissections.

3. He suggested that each student see as many different dissections as possible.

4. He urged the beginning students not to spend time taking notes but rather to devote their entire time to the lecture and demonstrations. In the second course, he advocated the taking of notes and even suggested that such notes be carefully revised.

5. He knew that some pupils enroll just "to go through a prescribed form of education" and are not interested in acquiring knowledge. He insisted that such persons must not disturb students who wished to learn the subject of anatomy.

6. He requested that the students not discuss the work of the course with the general public, "especially with regard to dead bodies." The morbidly curious were not to be allowed to visit the school.

That much of William Hunter's claim to a place of prominence in the history of anatomy is due to the fact that he trained his brother John has often been stated. As long ago as in the Hunterian Oration for 1837, Sir Benjamin Brodie, who was a former teacher at Great Windmill Street School, said, in referring to William Hunter:

He brought the uncouth Scotch lad to London, who afterwards became one of the greatest philosophers of this country, but who might otherwise have remained to be a farmer in his native county of Lanark.⁷

Much has been written about John Hunter (1728-1793) over the years. The Hunterian Orations, delivered (with a few exceptions) annually from 1814 to 1853 and every other year since 1853, have covered a wide field of topics related to John Hunter. Biographies of the younger brother continue to be written and to attract many readers.^{14,15}

John Hunter is remembered not only for his contributions to anatomic knowledge but because he was a great teacher who gathered about him pupils who made their marks in the world. Astley Cooper, John Abernethy, Edward Jenner, and Hunter's nephew, Matthew Baillie, became leaders in British medical circles. John Morgan, William Shippen, and Philip Syng Physick from the New World returned to this country to become leaders in medicine. A brass plaque placed on Hunter's grave in Westminster Abbey in 1862 by the Royal College of Surgeons of England records "its grateful veneration for his services to mankind as the founder of scientific surgery."

SOME AMERICAN PUPILS

Thomas Bulfinch, one of Cheselden's pupils in the winter of 1718, is said to have been the first American to study under him. He completed his medical studies in Paris three years later and returned to Boston.⁴

Thomas Cadwalader (1708-1799),¹⁶ a Philadelphian, studied anatomy under Cheselden in London. On his return to Philadelphia, he conducted classes in anatomic dissection and had a large number of students. Cadwalader is remembered as the author of what is generally considered to be the first medical monograph published in this country. His monograph, *An Essay on the West India Dry Gripes, to which is added an extraordinary case in physic*, was printed by Benjamin Franklin in 1745.

Cadwalader was a consulting physician to the Pennsylvania Hospital. This institution was established in 1751 largely because of the efforts of Thomas Bond and Franklin.

*Silvester Gardiner*¹ of Rhode Island, another pupil of Cheselden, gave anatomic lectures at the meetings of the Medical Society in Boston. An ardent Tory, Gardiner fled to Halifax at the time of the British evacuation of Boston. His drugs were confiscated by John Morgan for the use of the Continental Army. The town of Gardiner, Maine, bears his name. He had been the owner of large tracts of timberland in that area.

James Lloyd (1728-1810)¹⁶ of Boston spent two years in London. He worked under Cheselden, studied midwifery under Smellie, and attended William Hunter's anatomic lectures. He became a close friend of John Hunter, who was his brother's assistant at that time. This friendship lasted over the years. On his return to London more than forty years later, Lloyd was warmly received by Hunter.

Lloyd, because of his ability, drew many students who studied anatomy and surgery under him. Major General Joseph Warren, the physician killed at Bunker Hill, was one of his pupils. He, in turn, had had much to do with the medical training of his brother, Dr. John Warren, who was Harvard's first professor of anatomy (1783) and the first president of the Massachusetts Medical Society.

John Redman (1722-1808)¹ studied for a year at Edinburgh under Monro primus, spent a year at Guy's Hospital in London, and completed his medical studies at Leyden, where he received a medical degree at the age of 26. It is said that he had more young men apprenticed to him for the purpose of studying medicine than any other Philadelphia physician of that period.

John Jones (1729-1791)⁴ began the study of anatomy in the classes of one of Cheselden's American pupils, Thomas Cadwalader. He continued his medical studies in London with William Hunter and Percival Pott; he also attended classes in Paris, Leyden, and Edinburgh. He began his medical practice in New York City. During the French and Indian War, he served as a surgeon in the Provincial troops. He occupied the chair of surgery in the Medical School of King's College, New York, at its establishment in 1768. Subsequently, he returned to London and took further work under William Hunter. He is especially remembered for his textbook, *Plain, Concise, and Practical Remarks on the Treatment of Wounds and Fractures*. This book, published in 1775, was called "the surgical text of the American Revolution," for it was widely used at that time. An appendix to the book deals with camp and military hospitals. It was the first American book on military medicine.

Jones moved to Philadelphia in 1780 and was elected vice-president of the College of Physicians of Philadelphia in 1787. One of his surgical patients was Benjamin Franklin, who remembered Jones in his will. Another of his patients was George Washington.

John Morgan (1735-1789)¹⁷ of Philadelphia received his A.B. degree in 1757 in the first class to graduate from the Academy and College of Pennsylvania. An apprentice to John Redman

and an army surgeon in the French and Indian War, Morgan went to London in 1760 and studied under William Hunter. He went on to Edinburgh, studied under Cullen and the Monros, and received his medical degree in 1763.

During his five years abroad, Morgan had talked to persons in various countries about the organization of a medical school in connection with the College of Philadelphia. On his return to Philadelphia, he submitted his plan to the Board of the College on May 3, 1765, and it was approved. His address, "Discourse upon the Institution of Medical Schools in America," was delivered May 30, 1765. He had discussed this paper in London with John Fothergill and William Hunter.

Morgan was appointed to the first medical professorship in North America. William Shippen was elected professor of anatomy and surgery. The first medical degrees were granted in 1768. (Morgan was appointed Director-General of the Military Hospitals and Physician-in-Chief to the American Army in 1775. He was dismissed from this position in 1777 but was exonerated two years later by a Congressional Committee appointed to look into the matter.) Benjamin Rush (1745-1813), who had studied at the Great Windmill Street School in London after his graduation from Edinburgh in 1768, became professor of chemistry in the new medical school on his return to Philadelphia in 1769. He was one of the signers of the Declaration of Independence in 1776.

William Shippen, Jr., (1736-1808)¹⁸ was the son of a Philadelphia physician and a member of a family prominent there throughout the colonial period. His father had taken great interest in Thomas Cadwalader's course in anatomy, the first in which the subject was taught by dissection in that city.

William made an excellent record at the College of New Jersey. After an apprenticeship served with his father, William studied under John and William Hunter in London, as well as with William Hewson. At Edinburgh, he had William Cullen and Monro secundus as his teachers. He received his medical degree there in 1761. On his return to his native city, he began to conduct classes in anatomy on November 16, 1762. His first lecture at the State House drew a large crowd of Philadelphia's intelligentsia. His first regular classes, for which 12 students registered, were held at his father's house. For three years, he conducted his private classes in anatomy. In March 1762, he began the first systematic teaching of obstetrics in the American colonies. Not only his study under William

Hunter but also the instruction he had received under George McKenzie of London gave him an interest in, and knowledge of, midwifery.

Shippen joined with John Morgan in founding the medical school of the College of Philadelphia and was professor of anatomy and surgery at that school. He succeeded Morgan as Surgeon-General of the army in 1777. His military service brought problems which have been discussed at length by Middleton.¹⁸

Shippen resigned January 3, 1781, and continued to teach until his death from anthrax on July 11, 1808. Benjamin Rush's entry in his *Commonplace Book* for that day refers to Shippen as a teacher of anatomy, "in which he was eloquent, luminous and pleasing."¹⁶

Philip Syng Physick (1768-1837)¹⁹ was also a native of Philadelphia. His father, during the colonial period before the American Revolution, had served as Keeper of the Great Seal of the Colony of Pennsylvania. He had received his baccalaureate degree in arts at the College in Philadelphia and then served an apprenticeship with Adam Kuhn (1741-1817), who had studied under the Hunters and received his degree at Edinburgh. Like his preceptor, Physick went to London and was a house pupil of John Hunter at the same time as Edward Jenner. Hunter wanted Physick to stay in London as his assistant, but he went on to Edinburgh and received his medical degree in 1792. For thirteen years, he served as professor of surgery at the University of Pennsylvania and then, from 1819 until he resigned in 1831, he occupied the chair of anatomy. He has been called the "Father of American Surgery."

Caspar Wistar (1760-1818)^{16,20} first studied under John Redman and John Jones. He graduated from the medical school of the University of the State of Pennsylvania and later (1786) received the M.D. degree from Edinburgh. In 1792, he was elected adjunct professor of anatomy to Shippen at Pennsylvania. He prepared specimens and models which later formed the first collections of the Wistar Institute. His interests were not only in anatomy; geology and botany held a great fascination for him. The wisteria vine was named for him by Nuttall.

Wistar's "System of Anatomy" was the first textbook on anatomy published in this country. His name lives on in the Wistar Institute of Anatomy and Biology in Philadelphia. His grandson, General Isaac Wistar, presented the building for anatomic preparations and research.

SUMMARY

The early teachers of anatomy in this country

were principally trained by men in London and Edinburgh. The influence of the University of Edinburgh and of proprietary schools established by the Hunters in London, particularly Great Windmill Street School, were especially great. Men from the American colonies returned from study abroad and started classes in anatomy. Not until 1765 was a medical school established in the Colonies. Its first professor of anatomy had been a pupil of the Hunters and Monro secundus.

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Some Contributions by Anatomists to Endocrinology

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I AM indeed honored to be asked to write a short manuscript on the roles anatomists have played in the field of endocrinology. Anatomy became the first scientific discipline in the art of medicine. This may be one reason why anatomists have contributed so much to many phases of scientific research. Anatomists who have developed those subjects basic to the medical specialty of endocrinology have contributed not as endocrinologists treating patients, but as scientists concerned with such basic phenomena as the analysis of menstruation, ovulation, and secretion of hormones. Studying endocrinopathies, for example, may be a means for securing knowledge concerning fundamental processes related to hormone functions. However, the opposite probably is just as true—that is, that basic science has led to a greater understanding of endocrine disease. Furthermore, it is difficult to confine the parameters of endocrinology to the ductless glands themselves because hormones influence functions of all cells.

When I first agreed to accept this assignment, I had no idea that it could be such a formidable task. The amount of time available to prepare such a manuscript and the limitations of space forbid mentioning, let alone giving in detail, numerous contributions which anatomists over the years have made to endocrinology. Indeed, when I began to assemble names of some of the outstanding figures who have laid the groundwork for modern endocrinology, it became evident that a tome of some dimensions would be needed to simply recount the importance of the discoveries that have been made by anatomists. To give credit to all is impossible and, therefore, it is necessary to confine these thoughts to certain milestones in the development of our knowledge of the endocrine system and of the actions of hormones. The early histologists and, before them, gross anatomists described the various

glands which later were classified as endocrine glands. The realization that these organs did not secrete by way of ducts but directly into the blood stream was recognized early by embryologists and histologists, who called them endocrine glands as opposed to those with a duct system, the exocrine glands. Anatomists have been active in research which laid the groundwork for modern functional concepts of endocrinology since the beginning of this century.

To give some order to recounting a few of the major accomplishments of anatomists in the development of endocrinology, the subjects will be divided according to the chemical nature of the hormones.

STEROID HORMONES

The greatest amount of effort in endocrine research has probably been exerted in investigations of steroid hormones. Their source, chemical structure, and modes of action have been the objects of attention by a wide variety of scientists. These hormones fall into two large categories: those which influence primary and secondary sexual characteristics and those which influence mineral, protein, carbohydrate, and fat metabolism. The first group is derived from cells indigenous to the ovary and testis; the second group of hormones arises in the adrenal cortex. It is of some interest that cells which elaborate all the steroid hormones arise from the same area of the genital ridge.

ESTROGENS AND GESTAGENS

When truths become well established, it is difficult to realize that man has not always known them. The period since the discovery of hormonal influences on estrus, progestation, ovulation, and menstruation is not great (1913) but the over-all picture of these events and many of the hormones controlling them are well elucidated. Most of these events were discovered and their cycles worked out by anatomists.

Among these early contributions, the roles played by the endocrine organs regulating sexual

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functions were emphasized by George Corner, Philip E. Smith, Herbert M. Evans, and John H. Long. Corner traced the development of the corpus luteum and demonstrated that its secretions played a role in implantation and the maintenance of pregnancy. Much of this work was performed on pigs at various stages during gestation. Evans and a colleague, Smith, who performed some of the earliest studies on the pituitary gland, were among the first to demonstrate the effects of hypophysectomy in the rat. These anatomists were also among the first to demonstrate the phenomena of ovulation and the necessity for the pituitary secretions in the production of follicles and corpora lutea. At the same time, similar work was being performed at Bristol by Sir Solly Zuckerman, a British anatomist.

Long and Evans also pioneered investigations on the rat estrous cycle. While working on the pituitary and studying its effects on growth and the maintenance of various target organs, vitamin E was discovered by Evans as a by-product of this work. Over these many years, Evans has continued to be one of the most productive investigators in all aspects of endocrinology; indeed, just a list of his accomplishments would be too long for the present discussion. Anatomists not only studied the changes in the structure of the endocrine organs but also the relation of hormones to metabolism and growth. They have delineated in many ways specific peripheral actions of all the hormones.

Anatomists introduced the concepts of ablation of endocrine organs and then, by crude methods, the re-establishment of function by replacement therapy. Their discoveries of specific loss of function and its repair laid the groundwork for assay methods and, thereby, the isolation of purified hormones. For example, if the estrus cycle had not been studied as thoroughly as it was, it would have been difficult for later investigators to evaluate the actions of highly chemically purified steroids obtained from the ovary. It seems that this example may be generally true throughout the whole field of endocrinology.

Edgar Allen and E. A. Doisy worked for many years to determine the source of estrogenic hormones. In turn, their work complemented the anatomical work of other anatomists who studied histological changes during the estrus cycle and sexual cycles of the human, leading to development of an assay method for the evaluation of functions of extracts of the ovary and of the follicular fluid. This later culminated in the work of Doisy who characterized the chemical structure of the estrogenic hormone. G. N. Papanicolaou,

who is now famous for his smear technic for diagnosis of cancer, used this technic to characterize the sexual cycle in the human female as early as 1933.

The influence of steroid hormones on the growth of the ducts of the mammary gland and the establishment of lactation are also subjects of anatomical research. The roles played by estrogens in lactation and the production of mammary cancer were studied extensively by W. U. Gardner and his colleagues. The mechanisms of regression of the active glands following lactation are important with respect to possible subsequent pathological changes. Histologists such as Lane Williams have contributed much to this subject.

Some of the first, and still most important, investigations of the physiology and induction of menstruation were performed by anatomists. For example, J. E. Markee transplanted monkey endometrial tissue intraocularly into the same species and was able to observe the changes which occurred with suitable hormone treatment. His research established the important role of the minute arterial supply of the endometrium in menstruation. Smith and E. T. Engle pointed out that the ratio of estrogen and gestagen levels was related in time dependency to the onset of menstruation, and his finding has acquired such firm status today that many do not realize it was not initially a clinical observation. The development of a decidual response assay method by Charles Hooker and Thomas Forbes has considerably furthered the study of endometrial responses and also the knowledge of structure activity relationships of gestagenic hormones. Histochemical investigations of the endometrium by G. B. Wislocki, E. W. Dempsey, W. B. Atkinson, and others have contributed to our knowledge of how hormones influence endometrial cell composition. The influence of progesterone on glycogen deposition by endometrial cells was also demonstrated histochemically by Atkinson. The author is particularly interested in the fact that cortisol produces an epithelialization of fibroblasts and an increase in their polysaccharide content throughout connective tissue. This action of the cortisol on fibroblasts in general is similar to the effects of progesterone on the epithelialization and glycogen deposition in uterine fibroblasts and gland cells.

Other investigations, not immediately related to functions of steroid hormones but to the problem of ovogenesis, are still being pursued. The question of whether ovogenesis from the germinal epithelium occurs throughout life is still, in the author's opinion, not completely settled.

The work of several anatomists, such as H. M. Evans, Olive Sweazy, John Latta, and others, tends to suggest that germinal epithelium is continuously differentiating although the Aschner theory seems to be predominantly held today.

ANDROGENIC HORMONES

Most of the anatomical investigations of androgenic hormones are concerned with their cellular site of origin, their effects on secondary sexual characteristics, and, finally, on growth, development, and maintenance of various tissues. It has become quite apparent that the interstitial cells of the testis are the main, if not the only, site of androgenic hormone production. Early morphological evidence for this was provided by Rasmussen and others. Dempsey and Wislocki showed by histochemical evidence that androgenic hormones could be present in the interstitial cells, although their technic is not a specific one. Hooker demonstrated the correlation between cyclic cytological epithelialization of fibroblasts and regression to stellate forms and the amount of androgen present in the bull testis. Carroll Pfeifer and Arthur Kirschbaum demonstrated the production of epithelial-like cells in the sparrow testis under influence of pregnant mare serum. These cells regressed to typical sparrow lymphocytes following cessation of treatment. There is some evidence that sertoli cells may secrete androgens, but the overwhelming evidence is in favor of the glandular role of the interstitial cell.

Probably the most extensive studies of the role of androgenic hormones on the extrasexual tissues of man have been made by J. B. Hamilton, an anatomist. Among other things he has demonstrated the role of androgens in hair-growth patterns and capacity to tan and has noted the short life span of the male of many species as compared with the female. The role of androgenic hormones in the development of the secondary sex organs and in the relationship of pituitary and androgenic secretions to the maintenance of spermatogenesis in the absence of pituitary secretions has been investigated by several anatomists. Warren O. Nelson demonstrated the necessity for a proper androgen-estrogen ratio to maintain and develop the musculature of the genital tract of the male. He also showed that androgenic treatment could maintain sperm production without the pituitary, if it is given immediately after operation.

THE CORTICOSTEROIDS

There probably have been fewer anatomists who have been interested in corticosteroid research

than in sex endocrinology. There has been, however, much research on the structure and blood and nerve supply of the adrenal gland. This has been well reviewed by Ernst Scharrer. The changes in the weight and specific gravity of the human adrenal gland were noted by C. A. Swinyard. He found that the gland undergoes rapid postnatal involution. This finding has acquired much medical significance in recent years since evidence indicates adrenal cortical insufficiency accompanies this loss in size.

Hans Selye, who developed the stress concept in 1937, was on the staff of a department of anatomy at that time. In addition to introducing the stress concept and the concept of the general adaptation syndrome in the production of various degenerative diseases, he performed many experiments in classical endocrinology which are models of the experimental method and are among the more solid contributions to the field of endocrinology. The observation that stressful agents produced a loss of sudanophilic material from the adrenal cortex was made by many anatomists. However, LeBlond noted that silver precipitating material also was depleted and suggested that ascorbic acid decreased following acute stressor stimulation. This finding was amplified and resulted in chemical methods used for assaying ACTH by Sayers, a physiologist, who established the basic methods for stress and ACTH-mediated, ascorbic-acid depletion.

Among the most important contributions in the field of adrenal cortical anatomy and physiology is the fact that different steroid hormones were secreted by different portions of the adrenal cortex. For example, Greep demonstrated that the zona fasciculata responded primarily to ACTH and to stress effects mediated by ACTH. Selye had shown some time previously that different hormones were secreted from the adrenal—those which had an effect on mineral metabolism or electrolyte loss or retention and those which primarily affected the production of glucose from protein stores. These he called the glucocorticoids as opposed to the mineralocorticoids. Greep demonstrated in hypophysectomized animals that, whereas the fasciculata underwent degeneration, the glomerulosa tended to retain its normal configuration to a great extent. By a series of ingenious experiments, Greep demonstrated that mineralocorticoids were produced by the zona glomerulosa, whereas glucocorticoids were primarily derived from the fasciculata. This observation of Greep's, which was not accepted entirely by endocrinologists at the time he enunciated it, has come to

be quite well established. Greep also demonstrated that cells from each of the zones gave rise to cells characteristically found in that zone, thus challenging the existing so-called "escalator" theory for the development of cells of the adrenal cortex from the fibrous capsule. This, however, in the author's opinion, is still not completely settled.

The author and his co-workers have demonstrated that certain of the corticosteroids possess the capacities to regulate lymphatic tissue growth and limit the extent of the inflammatory response. The structure activity relationships for these particular functions have been elucidated for known, naturally produced corticosteroids. Thus, it has been noted that, on the cortisol molecule, substitution at C-11 is essential for regulation of lymphocyte growth, maturation, and death, whereas a C-17 hydroxyl is essential for anti-inflammatory activity. Subsequent investigations in our laboratory have dealt with the mechanisms of action of cortisol in the events just mentioned, as well as the peripheral metabolism of cortisol by fibroblasts, lymphocytes, and reticulo-endothelial cells while this hormone is exerting its action upon them.

RELATION OF HORMONES TO CARCINOGENESIS AND CANCER THERAPY

The fact that some hormones, particularly certain steroids, are important in the production and possible treatment of some cancers was recognized by anatomists. Pioneers in this field were Allen and Gardner. These two men and their co-workers investigated the role of pituitary and steroid hormones as carcinogenic agents in mice, monkeys, and other species. The role of estrogenic hormones in the production of mammary cancer and lymphatic leukemia was a particular target of investigation. They also demonstrated the necessity for estrogenic stimulation for the production of mammary gland cancer in mice. Gardner, Kirschbaum, and I found that estrogens of a wide variety of chemical structures would induce lymphomas in various genetically homogeneous strains of mice.

Probably one of the most important discoveries was that some neoplasms are hormone dependent—that is, they will not grow unless a particular hormone is present. This was found to be true for a murine pituitary tumor by Gardner and for an interstitial cell tumor by Hooker. The concept of hormone stimulation or suppression of neoplastic growth should be explored much more intensely, since it has opened the door to an understanding of mechanisms by

which alterations in the internal environment can be responsible for induction and regulation of abnormal growth. It is conceivable that even radiation and virus induction of neoplasia may operate through hormonal mechanisms. Thus, the author and his colleagues have shown that malignant lymphocytes metabolize cortisol more rapidly than their normal counterparts. Such metabolic changes can be induced in normal lymphocytes by leukemogenic doses of x-rays.

NEURAL CONTROL OF PITUITARY SECRETIONS

The work of A. T. Rasmussen and his students on the hypothalamus and its relation to secretion of the anterior and posterior pituitary provided quantitative data of far-reaching importance. This group of investigators counted nerve fibers and cell bodies in the nuclei of the hypothalamus. They also studied the nerve supply of the anterior and posterior pituitary glands. Earlier, Rasmussen had counted the various types of cells in the normal and pathological human pituitary. I believe there is still insufficient use of the enormous amount of data made available by this group of workers in modern studies of the hypothalamus.

In this regard, one also remembers the classical work of David Bodian, who demonstrated that the median eminence contains cells capable of releasing the posterior pituitary hormones, and thus explained why hypophysectomy in the animal is not consistently followed by diabetes insipidus. Before Rasmussen worked on the hypothalamic area, he had performed classical studies on the hibernating gland. He followed the formation of the interscapular gland, showing how it developed during the period preceding hibernation. This area is composed of brown fat. Years later it was shown by Helen Wendler Deane, an anatomist, that the pituitary-adrenal-cortical secretions stimulated the development of brown fat. I made a similar finding and thought at the time that ACTH might be acting upon the production of brown fat without mediation from the adrenal gland. This was not extensively investigated, however, and more recently other contributors have suggested similar findings—that is, an extra-adrenal effect of ACTH.

The problem of the relation of the hypothalamus to the innervation of the anterior pituitary has been extensively studied by anatomists both in the United States and in Great Britain. It appears that, as far as the relationship of this region of the brain to the anterior pituitary is concerned, no one has been able to demonstrate with complete satisfaction any direct nervous

mediation. Apparently the hypothalamus may have a secretory mechanism which delivers secretions to the blood; these in turn stimulate release of hormone, particularly follicle-stimulating hormone (FSH), from the anterior pituitary. This problem has been studied by the British anatomists, DeGroot and Harris.

Anatomical investigations have shown that there is a portal system to the anterior pituitary so that blood is transported from the hypothalamic area directly into the anterior pituitary. In this respect, one recalls the work of Scharer who has demonstrated an actual neurosecretory mechanism. He has been able to follow secretory material from the hypothalamus down the stalk of the pituitary in some species.

PROTEIN HORMONES

The pituitary gland, both anterior and posterior, has been the object of numerous investigations which fall into 3 general categories. First are the anatomical studies (cytological, neuroanatomical) of the organ itself. Mention was made above of the functional importance of the blood and nerve supply of this gland. The cells of the anterior pituitary in practically all species have been categorized by anatomists. Second are the changes in the number and the morphology of the cells of the anterior pituitary under various experimental and pathological conditions. The major goal of much of this research is to ascertain which of the pituitary hormones are secreted by one of the morphologically distinguishable cells of the gland. The procedure used by many anatomists is to ablate a target organ in an experimental animal and then to determine the quantitative and qualitative changes which take place in the cellular population of the pituitary. Certain endocrinopathies and tumors of the pituitary have been found to be associated with changes in cell numbers and also with cytological alterations, e.g., basophil adenoma.

Investigations of this type are numerous and are based on the early work of Evans, Rasmussen, A. A. Konef, Smith, and other anatomists. In general, conclusions from these studies indicate that growth hormone, and possibly ACTH, are produced by acidophils. Gonadotrophic hormone probably is produced by basophils. At least 4 or possibly 5 hormones cannot be accounted for as being produced by a specific cell.

A third approach to pituitary function is to evaluate the effects of extracts of pituitary glands on various functions, particularly those lacking in hypophysectomized animals. By this means quantitative data may be obtained for

specific end-organ effects. This, then, allows means to evaluate the degree of purification of the protein hormone. Such investigations were started in several anatomy departments and are still pursued there. Probably the most famous investigations are those of Evans, Simpson, and Rhinehart on the discovery of growth hormone. Not only did this group discover the existence of this hormone, but they also performed most of the physiological studies on its function in growth and metabolism.

Experimental anatomists have worked on the effects of all the known pituitary hormones. They have provided the best assay methods for growth hormone, ACTH, prolactin gonadotrophic hormones, and thyroid-stimulating hormone (TSH). In view of the fact that credit cannot be given in each of these instances, it should be emphasized that almost every aspect of pituitary hormone function has been established by anatomists.

Anatomists have contributed to the study of the islets of Langerhans and the production of insulin, primarily through their studies of the cells which form the islets. They developed staining methods for differentiating the cells and classified them into acidophils and basophils. The cellular site of insulin production was determined to be the Beta cell. Among the most important contributions in this area by anatomists are those of Arnold Lazarow, who studied the mechanism of diabetes production of alloxan. This substance poisons the Beta cells and insulin production decreases. The correlation of Beta-cell damage and extent of diabetes has allowed a more quantitative approach to the study of this disease.

The parathyroid has been studied by anatomists primarily interested in osteogenesis with respect to the actions of parathormone on calcium metabolism in bone. Several anatomists have suggested that parathormone removes calcium from bone by stimulating osteoclasts to absorb calcium and deliver it to blood. This mechanism of action is not yet proved.

THYROID HORMONE

In addition to the classical gross anatomical, histological, and cytological studies of the thyroid, anatomists have contributed to thyroid research by formulating assay methods for TSH, by studying the secretory mechanisms of the thyroid cell and by developing radio-autographic methods for thyroid research. The assay method for TSH depends on the fact that the greater the amount of stimulating hormone, the greater the height of the thyroid cell. The stimulated cell

has been shown by DeRobertis to secrete by budding its cytoplasm directly into the follicle. The method of radioautography, developed largely by histologists, can be applied with great success in thyroid research, since I^{131} is utilized by the gland in forming thyroid hormone. By this means, the trapping mechanism for iodine can be investigated under various experimental conditions. LeBlond was one of the first to use this method. LeBlond and Cross were the first to use I^{131} iodinated thyroxin to study the release, disposition, and metabolism of this hormone in blood and many of the tissues of the body. This classical work has become of greater importance in recent years due to the interest in the comparative effectiveness of various thyroid hormones which depends on their distribution and rate of removal from blood.

SUMMARY

The main purpose of this report is to emphasize

that anatomists have participated at the most basic level of scientific investigation in endocrinology and, in many instances, have originated the research concepts. It is surprising that anatomists have performed such a large amount of the investigation on functional aspects of hormone actions. Many of the assay methods have been produced by anatomists as well. It is interesting that anatomists have participated in such diverse investigations in endocrinology. An attempt was made to emphasize this latter point by enumerating the variety of subjects studied. Perhaps the best example was not picked in each instance and perhaps important work was overlooked. However, the point to be emphasized is the range of research interests. Finally, it is intriguing that many investigators have worked in several different aspects of endocrinology and that some of them have made extremely outstanding contributions in each of these different fields.

VASODILATORS should be infused and oversedation and conduction anesthesia avoided in treatment of serious toxemia of pregnancy. The following regimen is recommended for patients (1) with sudden rise in blood pressure during labor or post partum, (2) with eclampsia and systolic blood pressure of 150 mm. Hg or higher, (3) with preeclampsia not benefited by other therapeutic measures, or (4) with hypertension and superimposed preeclampsia: intravenous infusion of a mixture of 20 mg. of hydralazine (Apresoline) and 5 mg. of cryptenamine (Unitensin) in 500 cc. of a 10 or 20 per cent solution of glucose is started at 20 drops per minute and gradually increased to 60 drops per minute. A Y tube is used for infusion, with one limb containing the vasodilator mixture and the other, plain glucose solution. Blood pressure is determined every five minutes for the first two hours and every fifteen minutes thereafter. Infusion is regulated to maintain blood pressure at 110 to 140 mm. Hg systolic and 60 to 90 mm. Hg diastolic. If systolic pressure falls below 100 mm. Hg, infusion of the vasodilator mixture is stopped and only the glucose solution is given, until pressure rises to the desired level. If pressure does not fall within thirty to forty-five minutes, another 1 mg. of cryptenamine is added for each 100 cc. of solution. If labor is to be induced, dilute oxytocic mixture is infused from a third bottle.

Sedation is provided by 20 cc. of 50 per cent magnesium sulfate injected intramuscularly, half of the dose in each buttock. As long as urinary output is more than 800 cc. in twenty-four hours, patellar reflexes are elicited, and respiratory rate is more than 14 a minute, injections of 10 cc. of magnesium sulfate may be repeated as often as necessary.

This regimen was used for more than 400 patients with toxemia of pregnancy and serious hypertension, including 73 with eclampsia; only 1 patient died. Treatment was continued for twelve to over one hundred hours.

M. L. McCALL: Severe toxemia of pregnancy. *Postgrad. Med.* 30:188-190, 1961.

Contributions by Anatomists to Clinical Neuroanatomy and Neurosurgery

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AT THE OUTSET of this brief account, it must be admitted that it is far easier to name specific contributions to neuroanatomy by men who were primarily clinicians than it is to say how and when anatomists have added to the diagnosis and treatment of diseases of the nervous system. For one thing, the full-time anatomist is, with rare exceptions, a fairly recent creature and, since his advent, he has been far more concerned with problems not immediately related to practice. Consequently, in the realm of the practical, and in terms of recognition, amelioration, or cure, the anatomist has had little to say and little to add. Could he claim that all neuroanatomy was the result of the efforts of a long and pure line of morphologists, the contribution would be both vast and obvious. But as anyone aware of history knows, such is not the case. Furthermore, it must in honesty be noted that all too often the anatomist has been either asleep or mistaken. Therefore, it might be advisable to note certain shortcomings and failures of this specialty before attempting some positive notes in its behalf. For instance, Gall, by all accounts was a superb anatomist but he is remembered chiefly as the founder of phrenology.

CURRENT CONTRIBUTIONS

Unfortunately for the history of anatomists, they were not the ones who unraveled the life history, and with it the mishaps and abnormalities, of the intervertebral disk. For centuries, they were content to acknowledge the presence of material between one bone and another and then direct their real efforts to the description of all and every detail of the individual dry bones. They thought it commendable to insist that a medical student learn to distinguish the first thoracic vertebra from all others because, lo and behold, it had both a full facet and a demifacet to "accommodate" the heads of certain ribs. So it was left to Schmorl, a pathologist, to call attention to the

pads between the bones and to point out that their course through life was not always an even one, that they could invade adjacent bones, and that they might even encroach upon the vertebral canal. But it was American neurosurgeons of the early 1930s who finally wove the work of Schmorl and their own experiences with "benign chondromas" into a fascinating and important addition to the tapestry depicting man's understanding of man.

Likewise, but in this case actively rather than passively, the anatomists were asleep in the field of peripheral nerve injury and repair. Over and over again they investigated this problem and came up with answers: plasma clots, sutures, arterial sleeves, and free grafts. All of these work very well in small experimental animals but fail completely at the clinical level, merely because man is a big animal with proper digital nerves as large as the sciatic in a full-grown rat. One cannot treat the human sciatic nerve like that of a rat and expect the same results.

Who but the anatomist should have advocated and introduced lumbar puncture, ventriculography, and anterolateral cordotomy, all simple procedures based on structure alone? However, Quincke, Dandy, and Spiller were not anatomists but men primarily concerned with day-to-day response to the needs of patients. One could go on almost without end to prove that anatomy, or at least anatomists, have had very little to do with current neurology at the practical level or with surgery applied to the nervous system. Almost every sign, every symptom, and all methods of treatment belong to the direct ancestors of those who practice medicine.

Is it appropriate then to discount anatomy and the anatomist as inconsequential or worse? The answer is, certainly not; but to support this assertion it is necessary to recall the past, since there is little in the present that would indicate a serious lapse or the slightest misstep in the world of treatment as the result of withdrawal of the contributions of all present-day anatomists. Equally apparent is the debt of all neuro-

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ogy to the tenuous, frequently interrupted, and still fragile chain of minds fascinated by the structure of the body, who see in form and its accurate depiction the beginnings of understanding.

HISTORICAL REVIEW

No one really knows who was the first anatomist, the first one to believe that much can be gained for the living by examination of the dead. All one can be sure of is that he long antedated Hippocrates. We know this because Hippocrates' first injunction to the novice was to study the bones as he and his predecessors had done for generations before him. It is conceivable, in fact, quite likely, that if Hippocrates were alive today he might wish to add atoms, molecules, neutrons, electrons, and protons to parts suitable for the beginner in medicine. But, however he might view the knowledge of today, it seems reasonably certain that the Father of Medicine would not fail to advocate that components and architecture are a necessary first for anyone aspiring to understand and to modify the vastly complicated and exquisitely delicate structure of the body. The history of the indifference of medicine to anatomy is a long and unproductive one, and not easily explained. Not long after Hippocrates, the Alexandrian Greeks, Herophilus and Erasistratus, introduced human dissection. Why was it that, after a very brief period, it vanished as a method until the Middle Ages? Even the study of human bones was apparently abandoned. Galen recommended that the student of medicine travel to Alexandria where such relics were available, and these words were written nearly five hundred years after the time of Herophilus. Without attempting to explain the mystery let us go on to another.

Galen, nearly 2,000 years ago, pointed the way to our times and ever so clearly. To do so all that he needed was an animal, simple tools, and ideas strange to his times. Galen was convinced and repeatedly avowed that there is no acceptable substitute for direct observation. Furthermore, he realized that some things could be understood only by the use of a living animal. As a result, he performed and recorded the first unequivocal experiment. When he cut the recurrent laryngeal nerves and the squeal disappeared, he used the essential synthesis of anatomy, physiology, and clinical know-how that has been used to wrest most of what is now known about the nervous system. By this one experiment, Galen paved the way for a steady conquest of the mysteries of neural function and malfunction, their detection, and their treatment.

Why was it then that men of medicine failed to build and progress on the work and advice of Hippocrates and Galen and, instead, went to sleep for centuries? We can be sure it was not a dearth of eager young people wishing to practice medicine or a lack of devotion to their patients during their active years. Forces beyond their control is the usual and probably correct answer, but one can wonder what might have happened if Galen had had immediate true disciples instead of admirers or if following him there had been a steady succession of those who dissected and described and who resorted to animal tests to prove their ideas. Without such men, medicine went blindly on for a thousand years. One who knew him is reminded of how often Professor A. T. Rasmussen was inclined to say that, if the anatomist had no other function, he served well in keeping the clinician sternly aware of morphologic reality.

Early in the sixteenth century Galen finally found a worthy successor. Appropriately he appeared as a reluctant, hesitant, but determined challenger of all Galen meant to medicine, but not what Galen actually was or intended to be. In Andreas Vesalius, the man from Pergamon finally found his true disciple and equal.

In neuroanatomy, Vesalius comes down to us as a very minor and inconstant foramen in the base of the skull. But equally so does he survive in history as one of the great iconoclasts, as a founder of much that we call up-to-date, and certainly as the greatest of all anatomists. By his own account, it was not easy for him as a very young and inconsequential figure in medicine to dispute with the learned men of his day. In their minds, what he had to say was as brash and revolutionary as anything one can conceive of coming from an intern of today. And what did he say? Merely, that reality, as witnessed by sight, touch, and smell, and particularly by sight, has ascendancy in medicine over belief and theory. As a record of his insight and his genius, he left, for all to examine, his "*De Corporis Humani Fabrica Libri Septem*," dated 1543. It still remains as the first and still unsurpassed example of visual education, a subject that learned educators of today speak of as new and a creature of their own invention.

More important, Vesalius succeeded where Galen failed in leaving behind him an unbroken succession of men who adopted his ways. Once issued, the "*Fabrica*" of Vesalius represented a challenge and not an answer to all who followed. They were quick to respond accordingly. Consequently, the years between our day and his have witnessed an unending succession of additions to

anatomy, including that of the nervous system, instead of endless commentaries on what Galen said. While one might dispute the role of the anatomist in all that has followed, it can hardly be denied that clinical neurology and neurosurgery would be blind and helpless without the descriptions, the charts, and the drawings of those who have preserved and perfected the grand design of Vesalius.

IMMEDIATE VALUE

On the other hand, one might sort, sift, and struggle with the facts of history and still have difficulty in establishing the immediate value of the professional anatomist in practical terms. Fortunately, this is not his task and, equally fortunate, is not what is expected of him by his clinical colleagues. For example, Santiago Ramón y Cajal, an immortal Spaniard, is and will continue to be admired and revered by the entire neurologic world for centuries to come. According to himself, Cajal was first, last, and always a morphologist and as such he contributed more than any of his contemporaries or his successors to the basic plan and all the exquisite detail of neural architecture. Over and beyond that, he endowed all he saw with movement and purpose. He never looked at a stiff and silver encrusted remnant without also seeing a mobile and purposeful bit of protoplasm that, in his day, had to be killed and abused no end in order to reveal the least of its secrets. He was not only a great anatomist but was the prophet and the champion of all who see form and function as coequal aspects of the mysterious ways of life.

Assuming that Cajal was the greatest of the neuroanatomists, one is still at loss as to how and when he contributed directly to the art and skills of clinical medicine. Perhaps his most direct relationship is via Hortega, Penfield, and Bailey, with a resultant clarity regarding diagnosis and prognosis of tumors of the brain. Probably Cajal cared less on this account because it was not his purpose to detect and treat disorders of the nervous system. His mission was to discover and elucidate design, to read, and to explain the blueprints as he saw them so that others might go on. With this as his goal, he was the grand master of modern neuroanatomy.

MODERN ANATOMISTS

But even the shortest of historical accounts is entirely misleading if it suggests that modern neurology rests on the labors of a few towering figures. Equally important are the major and minor contributions of thousands of less gifted and fortunate individuals. A. T. Rasmussen, in

his little book of 1947, *Some Trends in Neuroanatomy*, cites over 800 people who have in some measure contributed to neuroanatomy and the list grows longer almost by geometric progression. Since neither a detailed nor a panoramic review of the subject is intended here, one is forced to settle for some slight facet of the whole. Let it be borne in mind that Minnesota has not been barren in terms of neurology, and specifically neuroanatomy. By nativity and by importation, this state has been disproportionately fortunate as a locus of those who have contributed to man's understanding of the most complicated of all known entities.

Except for a mention of 2 names, the imports will be passed over in the belief that they will receive full and proper acknowledgment in a history of the University of Minnesota Department of Anatomy. To me, J. B. Johnston has always been a mighty legend, but Andrew T. Rasmussen is a living, enduring, and vibrant memory. It would be a profound compliment and a fascinating pleasure to write about the man who was for so many years Mr. Neurology at the University of Minnesota. One might well start with the stringy and imaginative boy in Utah who, one winter's day, set out in search of a lost heifer and who, near dusk, decided to give up and go home. As he recounted ever so many years after, only one more ridge separated him from the first white man's view of Bryce Canyon. Perhaps that cedar-laden ridge deflected him toward more important explorations than a gash in the earth. Surely, his later accomplishments earned him a more deserving place in history than that merited by the discovery of a natural and beautiful ditch.

It happens that Minnesota is the birthplace of some of the foremost students of the nervous system to which this country can lay claim. Clarence Luther Herrick and Charles Judson Herrick were born on a farm at what were then the outskirts of Minneapolis. Stephen Walter Ranson was born in Dodge Center, and James W. Papez came from Glencoe. Although not primarily a neuroanatomist, John Farquhar Fulton should be mentioned because he was a native of St. Paul and because, as a neurophysiologist and gifted medical historian, he had a keen appreciation for the place of anatomy.

Clarence Luther Herrick (1858-1904) will probably endure in history more through the writings of another than those of his own—in this case, a gifted younger brother. Like Socrates, he is dependent on a Plato for the perpetuation of his name and thoughts. C. Judson Herrick (1866-1960) proved over and over again that he was a

contributor of unusual merit in neurology. However, since he consistently and vigorously acknowledged his subsidiary position to his more greatly endowed and prematurely cut-off brother, one can best pay tribute to C. J. Herrick by perpetuating his conviction that his elder brother was one of the true pioneers and possibly the true founder of comparative neurology in the United States.

And what claim can be made for C. Judson Herrick himself? He never devised a neurosurgical procedure, he never detected and described a clinical sign, and he never dreamed of a beneficial drug. Should he then be dismissed as a contributor to the practical aspects of neurology? In all probability not, because even the most practical of clinical men requires a structural and functional basis for all he does. If none exists, he will either turn anatomist himself or dream up some imaginary structure or connection to explain what he sees and does. While he may be able to trace his methods and his conclusions step by step through an unbroken procession of his predecessors, he cannot in them find answers to basic questions that either plague or intrigue him. Should he turn toward all his teachers for these and recall the one who first focused his attention on the nervous system, it will be almost certain that this teacher was directly influenced by Herrick, who devoted much of his energies to *Necturus*, a lowly amphibian. But his real interest was not in a cold-blooded animal, but in why people act as they do.

Herrick, and his brother before him, realized that a direct assault on the basis for man's behavior might well lead to futility and confusion. Therefore, he looked toward the simpler creatures for a scaffold or prototype on which to build. Instead, he discovered that man is not unique and his individuality is shared by the most stereotyped of creatures, the ants. Not one of man's capacities is without a forerunner in far less complex creatures than primates. Thus, by the amphibian route, Herrick added greatly to what is known concerning the structural basis of behavior.

Stephen Walter Ranson (1880-1942) was a power in his contemporary world. Few or none were more influential in directing the course of neuroanatomy and few were his equal in attracting and training gifted students. Since they still are active and important, far beyond what numbers alone would dictate, it would be both unfair and unwise for one who is beyond the fold to appraise the work of Ranson in historical terms. Suffice it to say that he contributed to methods, added new information, and had a real place in

the development of modern concepts. One cannot say at this time whether Ranson will be remembered most for his textbook, his elucidation of the incidence and significance of the unmyelinated fibers of the dorsal roots, the revival of the Horsley-Clarke stereotaxic instrument, or the distinguished pupils he left behind him.

James W. Papez (1888-1958) will long remain an enigma in the history of neurology. His accomplishments range between the most pedestrian of anatomical recording to speculations that are far beyond the acceptable today. As it now appears, Papez's article, entitled "A Proposed Mechanism of Emotion," may go down as his most important though not necessarily his most original contribution. In this paper, Papez had the courage to proclaim that large parts of the central nervous system were used to add assessment of value to all other functions. While he recognized and appreciated the exquisite recording and interpretive powers of the visual system, the capacity of the temporal lobe to endow fantastically small energy values with meaning, and the enormous power of the frontal lobe to set the world on fire, he also recognized that this infinitely refined and complicated mechanism was lifeless, dead, and purposeless without feeling, without passion, without hope, and without belief. As a result he wrote, and wrote wisely, that the brain is not a computer but the ultimate organ of life.

CONCLUSION

So closes a response to an invitation to write concerning the contributions of anatomists to clinical neurology and to neurosurgery. And once again, as at the outset, it must be repeated that anyone attempting to do so does not have a wealth of practical advances to offer. Instead he must point out that before the neurologist and the neurosurgeon are clinicians, they are medical students and, to a greater or lesser degree, owe some of their own capacity to the anatomist. Furthermore, history strongly suggests that medicine might ride on unscathed for one generation, possibly two, with little attention and no deference to the anatomist, but, beyond that, the art and science of healing would drift ever deeper into the mists of the pre-Vesalian past.

Material and thoughts for this article have been drawn from Cecelia Mettler's "History of Medicine," A. T. Rasmussen's "Trends in Neuroanatomy," Haymaker's "The Founders of Neurology," biographical sketches in the *Journal of Comparative Neurology*, and last but not least, from the teachings of Professors C. M. Jackson, A. T. Rasmussen, and Richard Scammon.

Some Contributions to Hematology by Anatomists

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WHY SHOULD AN ANATOMIST be interested in hematology, of all things? This and similar questions have been asked of me not only by laymen but by many who should know that there is not really a conflict of interests. Rather than say that the individual does not comprehend the role of modern anatomists or appreciate the scope of hematology, the usual reply has been, "Because bone marrow is found within the medullary cavity of bones." It is indeed surprising to find out how many physicians still think of anatomists solely as dissectors of dead human bodies.

The concept of a modern anatomist has evolved from the times of Johannes Müller, Henle, and Kölliker, when the best anatomists were likewise the most important physiologists and great biologists. The former president of the American Association of Anatomists, H. Stanley Bennett, aptly said, before the seventh International Congress of Anatomists, "Though each anatomist has his own particular field of interest, the way of anatomy is broad. It is not restricted to the size of the structure studied nor to the species of plant, animal, or microbe under investigation."

Modern hematology is likewise a very comprehensive subject, investigated by morphologists, cytologists, geneticists, immunologists, biophysicists, protein chemists, coagulation workers, and rheologists, but some physicians restrict the term to the clinical or pathologic application of specialized research. Indeed, the field of comparative hematology is still largely unexplored, and the publication of an *Atlas on Avian Hematology* by Lucas and Jamros is a step in the right direction.

In a survey article, it is difficult not to miss some anatomists and slight others who have contributed to hematology. This is caused in part by the limitation placed on space. Another complication is that some anatomists change their

field of interest and become pathologists, physiologists, or clinicians.

By and large, American anatomists have contributed a great deal to hematology because they have been unrestricted in their approach. If all of the references in 2 monumental works—von Möllendorff's *Handbuch der mikroskopischen Anatomie des Menschen* and Downey's *Handbook of Hematology*—were checked, some contributions by anatomists to the general field of hematology might be missed, but we would certainly obtain an impressive sample.

THE EARLY ANATOMISTS

History tells us that Marinus, an anatomist in Rome about A.D. 50, thought blood was produced in the liver. It was over sixteen hundred years later that the early microscopists with crude lenses—Jan Swammerdam (1658), Malpighi (1665), and van Leeuwenhoek (1674)—paved the way for the development of hematology by examining red blood corpuscles from various animals. Leeuwenhoek may well be considered the founder of blood morphology, because he estimated the diameter of erythrocytes by comparing 100 of them with a grain of sand (1/30 in.). The shape of mammalian blood corpuscles was not determined for a long time afterward, because the compound microscope had to be devised and methods of maintaining isotonicity improved.

Johannes Müller (1834) first used the term red blood corpuscle and Kölliker (1845) described corpuscles as mostly biconcave or flat round bodies which had already been observed by Hewson (1777). Rindfleisch (1880) found that corpuscles, after losing their nuclei by extrusion, are at first bell shaped and later become biconcave disks from impact with others in the circulating blood. C. S. Minot (1900), F. T. Lewis (1904), Weidenreich (1905), and Radach (1906) described the cup-shaped erythrocyte as the normal form for the human adult, but Leslie B. Arey (1917) demonstrated that

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this concavoconvex cup was merely an occasional modification and that the shape of the red blood corpuscle depended largely on the osmotic pressure of the examining medium. A year later, Arey (1918) showed the same thing for the erythroplastid in the wing of the bat. Victor E. Emmel (1917) studied blood from a patient with sickle-cell anemia and found that elongated and sickle-shaped red blood corpuscles appear in sealed fresh preparations of blood after incubation. This phenomenon is still one of the chief diagnostic features of the disease. Emmel (1917) also showed that cells from the patient's father would sickle.

In recent times, Rebuck (1953) has been quite successful in demonstrating the 3-dimensional changes caused by the intracellular paracrystallization of relatively insoluble sickle ferrohemoglobin by electron microscopy. Let us not overlook the fact that nonnucleated hemoglobini-ferous corpuscles are found in some invertebrates and lower vertebrates. Emmel (1924) found that erythroplastids comprise between 90 and 98 per cent of the circulating red elements in *Batrachoseps*, a lungless amphibian. We are so accustomed to thinking of Nobel laureate Camillo Golgi as a neurocytologist and neurologist that we forget he observed the difference in the formation of rosettes in tertian and quartan malaria. Golgi also noted that paroxysms are coincident with sporulation of parasites.

The formation of erythrocytes from leukocytes was suggested by W. Hewson (1777), a student of John Hunter, but Kölliker (1845) was the first to note that the early precursors of the erythrocyte in the fetal liver were nucleated. Löwit (1887) first used the term erythroblast to denote these cells before their denucleation. Howell (1890) considered the latter process to be one of extrusion, while Emmel (1914) described it as a constriction. The process of nuclear expulsion involves a shearing stress and, to a certain extent, some extrusion (Pease, 1955), but it is really a process of abscission (Jones, 1959). Before proceeding any further, reference must be made to the excellent critical review on erythropoiesis by Michels (1931). There has been a surprising unanimity by Saxer (1896), Maximow (1907), Mollier (1909), and Neumann (1914) regarding the development of blood cells from the loose mesenchyme surrounding the hepatic epithelium. In the course of its development, the fetal liver contains varying amounts of hemocytoblasts, erythroblasts, granulocytes, megakaryocytes, mast cells, and phagocytic cells. Indeed, it is a superlative tissue for studying a number of cytologic problems. Kirschbaum and Downey

(1937) used this tissue in a study to compare some of the methods used in studies of hematopoietic tissues. Jones (1948) pointed out that the dry smear method of studying immature blood cells produces nuclear patterns formed by the sum total of nuclear and cytoplasmic alterations. This method seems to furnish a more sensitive indication of what a cell is doing than any other single known technic. Sorenson (1960) has shown in electron microscope studies that hepatic cells of the fetus could be readily distinguished from hematopoietic cells. He also observed the intercellular transfer of material, probably ferritin, from hepatic cells to erythroblasts. In similar electron microscope studies, Jones (1960) reported that some erythroblasts which invaginate the hepatic cells may be trapped within the cytoplasm of these cells, where they disintegrate and are digested.

ORIGIN IN THE BONE MARROW

Ernst Neuman (1868) described erythrocytogenesis in the bone marrow, but it was not generally accepted until much later. As a matter of fact, Charles Robin (1874), a distinguished histologist, considered that Neumann was encumbering science with his theory. The importance of this organ did not commence to be appreciated until its volume, variable distribution due to aging processes, and accessibility for diagnostic and therapeutic purposes had been determined. Bone marrow, which in the general sense functions as a secretory organ, averages 4.6 per cent of the total body weight, or 2.6 kg., according to Mechanik (1926). It may be said to rival or even surpass the liver in size as a gland. The relation of fatty to red marrow, the origin of blood cells, and the vascular pattern of the marrow are but a few of the interesting and important problems. Enderlen (1891), Hammar (1901), Retzius (1902), C. M. Jackson (1904), and Maximow (1907) were among the first to unravel some of these myeloid mysteries. C. M. Jackson (1904) in his contribution to the histology and histogenesis of the bone marrow, suggested that the marrow before the appearance of hemopoiesis should be called primary, at which time it consists only of reticular connective tissue and vessels. Downey (1913) was one of the first to confirm Wright's hypothesis for the megakaryocytic origin of blood platelets. The electron microscopic observations by Pease (1956) and Yamada (1957) also confirm this and the studies by Jones (1960) show that megakaryocyte granules develop within Golgi vesicles. Sundberg (1950) and Jones (1938) have studied the cytology of marrow cells in bone marrow

biopsies and sternal aspirations of patients with various blood dyscrasias. Weiss and Wislocki (1956) used the armadillo to demonstrate seasonal variations of normal bone marrow.

Dantschakoff (1907), Maximow (1907), Jolly (1907), Emmel (1916), and Sabin (1917) recognized that the first embryonic blood formation is intravascular and that some of the cells are derived from the primitive endothelium. This concept was applied to the adult bone marrow by Doan, Cunningham, and Sabin (1925), who considered the lining of intersinusoidal capillaries to be erythrocytogenic in health and disease. This interpretation was challenged by Adolph Ringoen (1929) (Downey's first doctoral student), Jordan and Johnson (1935) after studies with the light microscope, and more recently by Pease (1956) and Zamboni and Pease (1961) after electron microscope studies.

DIFFERENTIATION OF ANGIOBLASTS

Doan, Cunningham, and Sabin's hypothesis for hematopoiesis was based in part on an earlier study by Sabin (1917) on the differentiation of angioblasts in which she described a critical mitosis whereby the daughter cells were an angioblast and an erythroblast. Later, Sabin (1920) observed that, when the equator of the spindle of a dividing endothelial cell is parallel to the vessel wall, the outer cell becomes an endothelial cell and the inner one a megakaryoblast. Murray (1947) found, on two occasions, daughter cells which differed markedly from each other in cultures of rabbit thymus epithelium. In electron microscope studies on the chick embryo liver, Karrer (1961) has described what appears to be another example of critical or differential mitosis. These observations are in keeping with the unifying concept of the etiology of leukemia advanced by Osgood (1957) that one of the daughter cells must differentiate beyond the stage at which it is capable of dividing and the other must remain immature to divide again. The late Arthur Kirschbaum was one of the most vigorous and stimulating investigators of experimental mammalian leukemia.

Quite contrary to Doan, Cunningham, and Sabin's view, there is not one grand series of red blood cells beginning in the yolk sac and continuing even through adult life in the marrow. Dantschakoff's concept of a primitive and definitive series of red blood cells during embryonic development of the chick has been adequately confirmed by Maximow (1927), Dawson (1936), and Jordan (1938). The same concept, which also holds true for mammalian erythropoiesis, has been confirmed repeatedly by Maxi-

mow (1927), Bloom and Bartelmez (1940), Knoll (1929), Kirschbaum (1937), Jordan (1938), and Hamre (1947). C. S. Minot (1912) suggested a classification of erythroblasts according to their phylogenetic significance which referred to the primitive cells as ichthyoid and the definitive ones as sauroid.

Kirschbaum (1937) and Jones (1938), after studying primitive erythroblasts from various embryos and comparing them with megakaryoblasts in pernicious anemia bone marrow, concluded that the embryonic cells are similar to the pathologic forms but not identical with them. Genuine megakaryoblasts have a definite message for the clinician. Jones (1950) was able to show in experiments on the placental transfer of antianemic substances that primitive erythroblasts differ both chemically and physiologically from megakaryoblasts because they respond to high doses of iron alone. Block (1946) found that intraocular transplantation changes the hematopoietic processes in the embryonic yolk sac. Buckman (1961) observed that yolk sacs from goats, pigs, sheep, and cattle also produce normoblasts similar to those Bloom and Bartelmez (1940) have described for man. Sorenson (1961) has studied the rabbit yolk sac by electron microscopy.

Downey (1938) wrote that "Progress in the practical phases of all science depends on adequate knowledge and appreciation of the fundamentals on which the subject is based, and hematology as a branch of biological science is no exception." The origin and relation of blood cells under normal, experimental, and pathologic conditions are fundamental problems which, although they have engaged the curiosity of many anatomists in the past, are being investigated today quite vigorously with modern techniques. Studies by Maximow (1909), Weidenreich (1911), Dantschakoff (1916), Dominici (1920), Jolly (1923), Latta (1924), Jordan (1926), Kingsbury (1932), and W. Bloom (1938) have, in general, supported the unitarian theory. On the other hand, the studies by Cunningham, Sabin, and Doan (1925), based on the appearance of cells in supravital preparations, support the polyphyletic theory. In this connection, it should be pointed out that E. V. Cowdry (1914) observed the vital staining of mitochondria in blood cells by Janus green B; Herbert M. Evans and K. Scott (1921) noted the differential reaction of connective tissue cells to neutral red; Miriam Simpson (1921) studied the reaction of living leukocytes to more than 200 different dyes; and Florence Sabin (1923) made the first thorough analysis of human blood cells with supravital dyes. The polyphyletic view had already been

advanced by Stockard (1915), who claimed that an invisible difference in parent cells determined the destiny of the cell to form either a leukocyte or erythrocyte. Slominski (1927), by using a pseudoperoxidase reaction for hemoglobin, showed that primitive erythroblasts are derived from mesenchymal cells which were already differentiated. Paul Weiss (1959) believes "that in the higher animal, except for the germ cells, all somatic cell lines are specialized to some extent and, therefore, in postembryonic stages no truly undifferentiated cells exist." Brecher and associates (1961) have shown that, after continuous intravenous infusion of an isotopic precursor (tritiated thymidine) for DNA, there may exist in the normal rat more than one class of small lymphocyte. This, in contemporary parlance, is an expression of morphologic difference at the molecular level.

REGENERATION OF LYMPHOCYTES

The problem of the regeneration of lymphocytes has many theoretic as well as practical aspects. Downey and Weidenreich (1912) were the first to show a direct relationship between the reticulum and developing lymphocytes. Ackerman and Knouff (1959) found that lymphocytes in the bursa of Fabricius may develop from sources other than mesodermal derivatives. Studies by Stasney and Downey (1935), Sundberg and Downey (1942), and Sundberg (1947) have supplied the morphologic mechanism for the appearance of altered lymphocytes in the blood of patients with infectious mononucleosis. The original paper by Downey and McKinlay (1923) is considered a classic on this subject. According to Downey (1938), lymphoblasts which are numerous in acute and subacute lymphatic leukemia do not participate in the normal regeneration of lymphocytes, and Sundberg and Downey (1942) found them to be rare in benign hyperplastic nodes. In other studies on the reticulum, Downey (1938) demonstrated that not all cases of leukemic reticuloendotheliosis are monocytic leukemias and that there are two varieties of the latter.

THE FATE OF LYMPHOCYTES

Quantitative studies of lymphocytes and lymphoid tissues are necessary for an understanding of their function under normal and pathologic conditions, most of which are discussed in the book by Yoffey and Courtice (1956). C. M. Jackson (1925) reported that hyperemic and atrophic changes in lymph nodes during inanition were reversed upon adequate refeeding. Kindred (1942) calculated that the intestinal

submucosa contains 3 times as many lymphocytes as are present in the blood. Andrew and Andrew (1949) reported a novel fate for lymphocytes through their differentiation in epithelium cells of the colon. Jordan (1939) found an accumulation of lymphocytes in marrow from patients with aplastic anemia which he interpreted to indicate a lack of maturation. Thoracic duct lymph output has been studied extensively and Reinhardt and Li (1945) noted that ACTH diminished it. Dougherty and White (1943) first observed the action of steroids on lymphocytes and Brown and Dougherty (1956) reported a diurnal cycle as related to adrenal activity. Brecher (1961) and Everett (1961) have shown that the pattern of lymphocyte labeling with tritiated thymidine strongly supports Gowan's hypothesis of extensive lymphocyte recirculation.

The question of what happens to hematogenous lymphocytes is still a challenging one. Ekola (1931), one of Downey's students, studied inflammation in the subcutaneous tissue of rabbits and was able to trace the origin of macrophages from the lymphocyte, plasmacyte, and fibroblast. Kolouch (1939), by using dry-fixed spreads of inflamed connective tissues, emphasized that inflammation must be studied within the first 14 hours or else the lymphocytic origin of mononuclear cells is largely obscured. Tompkins and Cunningham (1938) were unable to obtain transitional forms between these cells. Dougherty (1944), utilizing a dry-fixed imprint technic for studying inflammatory reactions of the brain, observed that the first reacting cells were lymphocytes which transformed to macrophages. Campbell and Good (1949) found that lymphocytes transformed into intermediate polyblasts and later into macrophages during the antigen-antibody production in neurotropic virus diseases. Rebeck (1947) introduced a radically new technical procedure in which the cellular exudates of single lesions in man could be sampled periodically in skin windows. Rebeck (1955) showed that the transformation of lymphocytes into macrophages in man proceeds in an orderly fashion.

Intermingled with these studies are those of Kolouch, Good, and Campbell (1947) in which the differentiation of reticular plasma cells to Marschalkó plasma cells took 4 days after shocking a sensitized rabbit and a rising antibody titer was also noted. Leblond and Sainte-Marie (1960) constructed models for the formation of lymphocytes and plasma cells and concluded that the two series appear to be distinct and evolve independently. On the other hand, Tompkins (1960) believes that plasma cells of the

Marschalkó type can, and do, arise from small lymphocytes with atypical histochemical features within the nuclei. Electron microscope studies by Sorenson (1960) suggest that there may be an intercellular transfer of material between plasma cells and macrophages in lymph nodes. MacCardle (1960) found 3 types of Golgi apparatus in plasmacytomas of mice and Dalton (1961) has made electron microscope studies of the Golgi zone of lymphoma cells grown in mouse peritoneal fluid.

Fifty years ago, although Downey (1911) was reluctant "to add to the voluminous literature on the plasma cells," he pointed out that they are secretory cells and may transform into mast cells. Today there is electron microscope evidence to support Downey's view on the nuclear participation in mastgranulopoiesis. Downey (1913) subsequently studied the development of basophil leukocytes in guinea pig bone marrow and suggested to Nicholas Michels that he should investigate this problem in the lower vertebrates for his master's thesis. Michels (1938) published a 140-page chapter in Downey's *Handbook* which listed 25 different hypotheses concerning the function of these cells. Since that time there has been a tremendous upsurge of interest in these cells because of their relation to heparin, histamine, hyaluronic acid, and serotonin. Paff and F. Bloom (1949) studied the release of heparin in mast cells cultivated *in vitro*. Fawcett (1954) and Hunt and Hunt (1960) have used compound 48/80, a potent histamine liberator, to investigate mast cell function. Burton and S. Bensley (1958) reported that the fine structure of developing mast cells as revealed in electron micrographs distinguished them from other connective tissue cells. According to Priest, Rebnick, and Havey (1960), ulcerative colitis and interstitial cystitis predispose an increased extravasation of blood basophilic leukocytes in inflammatory exudates in human skin windows.

STRUCTURE AND FUNCTION

Early in this century the problem of determining the chemical composition of blood cells with the aim of correlating structure and function was investigated by Pappenheim (1911) and later by Sabin (1923) and her co-workers with the development of the supravital technic. The recent increase of interest in cytochemistry as applied to hematology has been due to the stimulating work of Lison (1936) and to the discovery of appropriate chemical methods for analyzing cellular composition or constitution. Tissue mast cells and basophil leukocytes are the classic examples of cells exhibiting metachromasia. Wislocki,

Bunting, and Dempsey (1947) and Rheingold and Wislocki (1948) found that these cells resist digestion in ribonuclease and hyaluronidase, which suggests that the metachromasia may be due to heparin. Montagna and Noback (1948) reported the presence of phospholipid, peroxidase, and lipase in these cells.

In general, Baillif and Kimbrough (1947), Wislocki and Dempsey (1946) Rheingold and Wislocki (1948), and M. Bloom and Wislocki (1948) found that information obtained from studying blood cells stained with Sudan black B parallels that from the peroxidase reaction. Basophils have some sudanophilic granules varying in size and their intensity of staining. Noback and Montagna (1946) did not find glycogen in mast cells, but Wislocki and his co-workers and Leblond (1950) found it in segmented neutrophils, metamyelocytes, and some myelocytes and megakaryocytes. J. D. Boyd (1960) reported that megakaryocytes in human fetal livers possess large amounts of PAS-positive, diastase-resistant material in their cytoplasm. According to Ackerman and Knouff (1960) this material appears even before primitive megakaryocytes can be recognized by the usual morphologic criteria with the light microscope. Ackerman (1950) demonstrated that Auer bodies in leukemic cells are oxidase, peroxidase, and PAS positive; sudanophilic; slightly metachromatic; and positive for acetal lipids and ribonucleic acid.

CELL CULTURE

Ross G. Harrison (1907) first demonstrated that tissue cells can grow after excision from the body. The tissue culture technic in the hands of Dantschakoff (1909), Margaret and Warren Lewis (1911), Champy (1912), Maximow (1916), Erdmann (1917), Chlopin (1922), W. Bloom (1927), and Parker (1932) has done much to unite morphological and physiological concepts in hematology. Studies on the manner of locomotion of blood and tissue cells *in vitro* led Rich, Wintrobe, and Lewis (1939) to conclude that myeloblasts, lymphoblasts, and mononuclear phagocytes were unrelated. DeBruyn (1945) was able to show in cultures of abdominal lymph nodes from rabbits that lymphocytes migrate in two phases. He established a genetic relationship on the basis of gradual transitional stages in the mode of migration between the typical lymphocyte and the hypertrophied lymphocyte and between the latter and macrophages. Berman (1942), a pathologic anatomist, described a method for obtaining dry films from tissue cultures of rabbit lymph nodes in which there was a marked transformation to macrophages after

31 hours. Goldstein (1954) observed an accumulation of PAS-positive material during giant cell formation. Porter, Claude, and Fullam (1945) described in electron micrographs of fibroblasts cultured *in vitro* a lacelike reticulum which formed the basis of studies by Palade and Porter (1954) of a cytoplasmic component which is known today as the endoplasmic reticulum. The relative proportions of this and other cytoplasmic organelles are shown in the atlas by Low and Freeman (1958) on electron microscopy of blood cells.

The era of morphologic hematology is not finished, nor are the newer technics a panacea for

our morphologic difficulties because even they, in some instances, require a greater refinement of our observational powers.

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THE STRING impregnation test detects and locates active ulceration and erosion of the upper digestive tract with satisfactory accuracy. Simple, convenient, economical, and without complication, the test can be used for both diagnosis and subsequent appraisal of upper digestive tract bleeding and obviates repeated roentgenographic examination in the management of duodenal peptic ulcer. In patients without radiologic signs of disease, diagnosis of upper digestive tract lesions may be confirmed if the string test reveals bleeding and symptoms subside after treatment with antacids.

The test is done in the evening. After the 4-ft. string—soft cotton, 2 mm. in diameter, or narrow cotton umbilical tape—is moistened with water, the patient swallows one end weighted with a 0.8-cm., 2.2- to 2.5-gm. lead ball. Increments of 10 to 15 cm. of string are swallowed with sips of water until the reference knot, 10 cm. from the nonweighted end, reaches the lips. The impulse to gag is suppressed by deep mouth breathing. Inspection is made to be sure the string has not collected in the oropharynx. The free end of the string is fastened to the cheek with adhesive tape.

Only water should be ingested until the string is withdrawn in the morning. If the lead ball stops at the oropharynx as the string is removed, the patient gags or swallows to loosen the weight.

After removal, the string is inspected for stains. Application of guaiac test solution to the string aids assessment. Deep bile discoloration of the distal end is a reliable index of duodenal entry. Visible blood deposits may vary from faint stains to heavy clots of gross blood, but only grossly visible stains should be regarded as positive. The heavier the stain, the greater the likelihood of ulcerative disease of the adjacent mucosa. Location of a bleeding site may be inferred from the distance between the blood stain and the lips—15 to 40 cm. from the lips, esophagus; 40 to 55 or 60 cm., gastric mucosa; and beyond 55 to 60 cm., duodenal and jejunal mucosa.

Since the string may abrade the mucosa so that a blood stain appears, false-positive results are possible. A negative result in a patient with signs of gastrointestinal bleeding indicates that the bleeding arises from a point in the digestive tract distal to the end of the string or that a higher lesion has closed over.

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Contributions of Anatomists to Growth and Development

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THE SCOPE of growth and development includes the total organism over its total life span, from fertilization to senescence. Hence, these subjects occupy a central position between those disciplines concerned with segments of the life span and those concerned with the successions of many life spans. Most biologic fields examine the organism in a suspended moment of time (the fixed organism); in varying segments of time, including milliseconds (nerve conduction); in seconds to hours (digestion and respiration); or in major portions of the life cycle (migratory rhythms). At the other extreme are fields concerned with the geologic time scale (evolution and paleontology).

One essence of life is continuous change and, in turn, continuous change is the dynamic substrate of growth and development. In order to understand this change, students must integrate into their armamentaria information and data from all the biologic disciplines, including descriptive and experimental morphology, physiology, genetics, biochemistry, and biomathematics. The disappearance of the boundaries among the areas of biology in the current scene is a reality in growth and development.

In a general way, growth and development have been objects of man's curiosity since the time of the ancients, but the subject has been formally organized only recently. Embryology per se is considered to have been launched by von Baer in 1828, experimental embryology by Roux in 1883, and aging by Cowdry¹ in 1939. All phases of growth and development have expanded significantly in the number of investigators, the quantity of publications, and the quality of advances. Yet, a paradox exists today. In spite of the tremendous progress, formal instruction in the broad aspects of growth and development has been slighted to a large degree.

In a sense, anatomists have investigated the

interval in excess of the life cycle, for they have studied the maturation of the ovum and sperm before fertilization and have maintained cell populations—in tissue culture—beyond the donor organism's natural death. The anatomist uses morphology as a base of operations for forays into the living world. The statics of the past have yielded to the dynamics of today. However, anatomists should not neglect or spurn the usefulness of pure morphology. In effect, comparative morphologists use another animal species as a natural experiment. One may recall rather humbly that such geniuses as Cajal, Downy, and Retzius were able to abstract from morphology fundamental concepts that ramified far into the world of functional biology.

Electron microscopy is one of the many new techniques used by modern morphologists. The drive of the electron microscopists to reach the higher magnifications with greater resolution will eventually, with the aid of such future developments as a hydrogen ion microscope, enable them to achieve the molecular level of the biochemist and the biophysicist. Many biochemists consider classical biochemistry to be, in a sense, a 2-dimensional discipline. The spatial relation of the macromolecular complexes, 3-dimensional biochemistry, is forming the new basis for the integration of the biochemist's domain with the morphologist's world. Then the stage will be set for the fourth dimension, time. Growth and development are equated with time.

Only a few highlights in the field of growth and development will be mentioned. Many anatomists have contributed. The author extends apologies to those whose contributions have been omitted in reference but not in spirit.

PANORAMIC VIEW

The principle of progressive differentiation states that, in the development of an organism, each advance in development is dependent on the preceding steps and is, in turn, essential for future development. In 1908, the great anatomist Minot² theorized on the broad aspects of

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development and growth. Today, his thoughts are still provocative and stimulating. Growth and development are expressions of the aging process that is a continuous phenomenon commencing at fertilization and extending throughout the life cycle of the organism. The aging of any organism implies that the process of cellular differentiation is reduced with time, or, stated otherwise, the ability of cells to grow in size or to increase in numbers decreases with age. The main impasse is the obtaining of objective quantitative evidence to support this concept. For example, does a fibroblast have more mitotic potential in the young than in the old organism, granted that it is high at both ages? Minot's concept states that aging is more rapid in the young than in the old. This stems from his postulate that the specific rate of growth is a measure of the vitality of the organism.

The specific rate of growth is the rate of growth at any developmental stage divided by the size of that organism at that stage. This is a measure of the capacity of a structure to reproduce itself. It is high during early development and low after maturity. The human organism increases about 10,000 per cent during the first embryonic month, about 75 per cent during the second month, and about 10 per cent during the third month. The newborn child weighs about 5 per cent of the adult weight. Hence the postulate is that we age faster in our youth than in our declining years. The concept is not without its critics.

The succeeding phases of the life cycle in mammals include the germinal period, embryonic period, fetal period, circumnatal phase, infancy, childhood, adolescence, maturity, and old age.³ At the University of Minnesota, investigations on growth and development were carried out by a number of workers. Jackson⁴ was a pioneer in the field of fetal anatomy. Scammon,^{3,5} a pupil of Minot, attempted to synthesize the theories, concepts, and knowledge of the entire field of human growth and development.⁶ In this synthesis, a unique collection of material of the past one hundred fifty years was assembled, outlined, and annotated, but the immensity of the source material resulted in the assemblage of a mass of material that was unfinished except in his brilliant, intellectual mind. Commencing with the first volume this year, Boyd will publish a 5-volume edition of *The Major Patterns of Human Growth*, in which this subject will finally be integrated under one title.

Many colleagues and students of Jackson, Scammon, and Boyd have made contributions in

the qualitative, quantitative, and graphic iconometric analyses of developmental anatomy. Among these are F. L. Adair, R. B. Allen, E. L. Armstrong, R. F. Blount, E. A. Boyden, L. A. Calkins, A. L. Cameron, J. T. Cohen, W. P. Covell, H. L. Dunn, M. B. Grandprey, R. G. Grenell, E. S. Hegre, M. H. Hesdorffer, C. Hymes, J. A. Kittleson, A. D. Kleen, F. N. Knapp, H. B. Latimer, D. Lawrence, H. D. Leas, F. J. Lewis, M. L. Lindsey, H. Lippman, D. C. MacKinnon, C. H. Mead, J. C. Nanagas, C. R. Noback, G. J. Noback, E. Norris, C. E. Palmer, C. K. Petter, W. T. Peyton, L. Richdorf, H. C. Roe, L. Rogers, W. H. Rucker, J. H. Schaefer, G. H. Scott, O. B. Sheets, V. Spaulding, C. M. Spooner, C. A. Stewart, R. E. Swanson, C. A. Swinyard, L. J. Tiber, H. Wald, C. H. Watkins, E. H. Welch, L. J. Wells, H. A. Willmer, C. B. Wright, and A. A. Zimmerman.

To assess the degrees of immaturity and maturity of an organism, tissue, or cell in even qualitative terms is difficult. The solution to this question will mark a signal advance in the field of development. The biochemical approach should be promising. Chemically, differentiation implies the synthesis of new molecules, while growth implies the synthesis of additional molecules of the existing type.⁷ A change in the enzyme pattern of cholinesterase during differentiation is an example of the specific relation between a chemical entity (an enzyme) and a cytologic structure (the synapse).⁷ Stages of immaturity may be equated with biochemical and morphologic differentiations. Cytochemical, biochemical, and functional differentiations are all related temporally during development.⁸ At one critical period in the development of the cerebral cortex, several phenomena are correlated with the maturation of the cortical neurons: (1) cessation of the growth of the nucleus; (2) evidence of nuclear maturity; (3) appearance of a mature nucleolus; (4) initiation of rapid cytoplasmic differentiation, as indicated by the abrupt appearance and rapid elaboration of Nissl bodies and intense sprouting of processes; (5) respiratory enzymatic activities; and (6) neurophysiologic and electrocortical activity.⁸ The structural changes in the differentiating neurons during the ontogenesis of the cat's neocortex during the first postnatal month can be correlated with the changing electrocortical activities and evoked response patterns.⁹

Even the life span itself may not be determined by the biologic equivalent of a clock spring.¹⁰ Rotifers reared under carefully controlled conditions have a short life span if suc-

cessive generations are propagated from eggs acquired from old mothers. The longevity is increased if successive generations are propagated from eggs obtained from adolescent mothers.¹⁰ The fact that the longevity of females is greater than that of males has intrigued anatomists.

EARLY DEVELOPMENT THROUGH ADOLESCENCE

The ovum and sperm may be specialized or generalized cells. In one context, the ovum and the sperm are specialized products of the ovary and the testis, respectively. Unless union of the sperm and ovum occurs, these cells usually become senescent and expire.

In another context, these elements are generalized cells which transmit the essence of one generation to another generation through the totipotent zygote. In a few days, the zygote becomes an organism with a pulsating heart (late in the first month in man) and a functional nervous system (late in the second month).¹¹ The basic story of the development of the heartbeat occurs within a period of less than forty-eight hours from the initial heartbeat in the chick.¹² The heart rate is intrinsic to a species. When the mesodermal rudiment of the sinus venosus is interchanged between two species of *Ambystoma*, the donor rudiment becomes the pacemaker for the host heart and the pulsating rate approximates that of the donor species.¹³

Fundamental concepts of structural and functional significance during the development of the nervous system are penetratingly discussed by the master neuroanatomist, C. Judson Herrick.¹⁴ They apply to the anatomic and functional correlations of human fetal development.^{11,15} Herrick weaves his concepts of integration and analysis with Coghill's thesis that from the total pattern is individuated the partial patterns. Integration is considered to be the more general, basic, and primitive mode of functioning. The focal mechanism of the convergence of the structural and functional paths is expressed as an over-all pattern in the undifferentiated, stereotyped movements of early development. Analysis is the differentiation of the over-all pattern into the "separate and distinctive recognition of or reaction to the activities initiated from different sources."¹⁴ The total pattern is the significant mechanism in the early stages and continues to play an important role later. The local reflex, or partial pattern, is through development individuated out of the total pattern. Herrick felt that this principle of development prevails universally in vertebrates, including man. The Swenson-Windle concept that the partial patterns are basic and are eventually integrated into the total

pattern in all forms save possibly *Ambystoma* is the alternate view.¹⁶

The self-marker concept of Burnet and Fenner associated with the production of antibodies has had its significant impact on the understanding of the developing organism's ability to be aware of both "self and nonself." Essentially, the problem is to explain how, during development, the organism is able to evoke a mechanism by which it is able to distinguish between its own substrates and those of foreign organisms. "The tolerance to antigenic stimulation observed in the embryo gives way to the sensitivity in the adult. There is a transition period in which no reaction occurs; neither tolerance nor immunity is produced by antigenic stimulation at this time. Presumably the immune reaction is developing but has not yet reached a sufficient state of perfection to permit the typical production of adult antibodies. At birth, or hatching, this transition period is already reached, with few exceptions." The plastic phase of early embryonic life gives way to the nonplastic phase of late embryonic life.¹⁷

Formal experimental embryology has a long list of contributors. One phase of activity in this field is concerned with the general problem of regeneration—more specifically, with loss in this regenerative capacity in both ontogeny and phylogeny. In the urodeles, limbs will regenerate and grafted limbs will function. If grafted in locations where the graft is reinnervated by normal limb nerves, coordinated activity with the normal limb may result.¹⁸ The regeneration of the adult anuran limbs was only accomplished recently, after the quantity and quality of nerve regeneration into the stump was found to be instrumental in inducing such growth.¹⁹ This advance is illustrative of the significance of the continuing search for factors related to encouraging and inhibiting the regeneration of tissues and organs. The problems associated with limb regeneration in cold-blooded animals are in some way interlocked with the over-all problems of nerve regeneration, bone repair, physiologic regeneration in hemopoiesis and in normal cellular replacement phenomena, wound repair, and neoplastic growth in warm-blooded animals.

The critical stage of birth has been the bailiwick of anatomists. Respiration is an example. Intrauterine aspiration of amniotic fluid into the fetal bronchial tree, as a natural phenomenon, is demonstrable in the normal fetus. The changing topographic relations of the thoracic viscera during this period and the details of the development of the lung proper have been studied at

the University of Minnesota.²⁰ The cuboidal shape of the cells lining the fetal alveolus gives the appearance of a gland, and the unopened capillary networks lying between the coiled arterial capillaries produce tremendous resistance to the passage of blood.²¹ At birth, when the lung is subjected gradually to negative pressure, the epithelial cells first begin to flatten; then, suddenly, the process rushes to completion with the overcoming of some critical resistance. With the full expansion of the alveoli, alveolar sacs, and ducts, the epithelial cells now remain flattened.²² This is in turn accompanied by a vast increase in the pulmonary capillary bed, and with this the lungs accept the whole output of the right lung, previously shunted through the ductus arteriosus.²¹

The evaluation of chronologic stages of development and growth has introduced such helpful concepts as morphologic, physiologic or biologic, psychologic, social, and biochemical ages and others.¹⁹ The growth and development of the child and adolescent are areas of active investigation. Cross-sectional studies²³ and longitudinal analyses²⁴ of skeletal maturation are illustrative of the methods for obtaining objective criteria for the assessment of physiologic age during these periods of the life cycle.

MALFORMATION AND ANOMALIES

Development is a long, continuous, unfolding process that is basically under genetic influence interacting with a given environment. Interaction with the environment during development may unbalance the normal development and malformations may result. Until relatively recently, malformations in mammals were interpreted as being fundamentally associated with genetic defects and not with environmental influences. Mammals were considered to have developed prenatally in a relatively constant environment. However, a number of positive teratogenic environmental agents are now known.

Two facets of the malformation problem are the concepts of (1) the time specificity of the action of teratogenic agents and (2) the agent specificity associated with a constellation of malformations.²⁵ Time specificity implies that a teratogenic agent may be responsible for different malformations at different times of development. Critical developmental times are associated with the formation of specific anomalies. Maternal deficiency of folic acid in a pregnant rat results in newborn animals with cleft palates; if the folic acid-deficient diet is first fed at the tenth day of pregnancy, all young have a cleft palate at birth, but if the diet is first fed on the twelfth

day, no newborn has a cleft palate at term.²⁶ The state of differentiation of the reacting tissues to a deficiency is important, for the deficiency may be present at all times but may manifest itself only at a critical period. Agent specificity is associated with the fact that teratogenic agents usually produce an associated group of malformations.²⁷ The specific agent probably has its effect on some metabolic process and, in a specific way, alters the developmental pattern. Of clinical interest is the observation that actinomycin is a teratogenic agent when it is given to pregnant rats in quantities of about one-fourth the recommended therapeutic dose.²⁸

AGING

Many questions require answers if the life expectancy after 40, changed only slightly, is to be lengthened. To the embryologist, whose perspective is the beginning of the life cycle, normal development is primarily, but not exclusively, the progressive changes from fertilization to senescence. To the gerontologist, whose perspective is the other end of the life cycle, normal development is primarily, à la Minot,² the regressive changes from fertilization to senescence. In practice, both concepts are valid.

"Aging is, like all other phenomena, essentially a problem of cells and their tissue fluid environments."²⁹ The tissue fluid and the ground substance vary in the different parts of the body, and during the aging process, a progressive increase in the fibrous components occurs. Cowdry²⁹ suggests an extension of the basic concept of homeostasis—chemical equilibrium in the blood—to a second and supplementary concept of heterostasis—maintenance of like or steady states in different tissue fluids' environments throughout the body.

Some morphologic data on the aging organism at the organ level, the cellular level, and the subcellular level have been assembled by many anatomists. The organs of lymphatic tissues are altered during the aging process.³⁰ The conspicuous light areas in the nodules of lymph nodes and spleen of young and middle-aged human beings and laboratory animals are smaller in size and reduced in number in old age. An organ with a short life history is the placenta, which functions during early development only to be discarded at birth. Its rapid aging is evidenced by the accumulation of calcium and the adaptive functional changes in the trophoblastic layers.

Cells have their own life cycles from mitosis to mitosis or mitosis to death. They do not all age at the same rate. Vegetative intermitotic cells—

the cells that exist only between cell divisions—are poorly if at all differentiated and do not exhibit senescence (spermatogonia and basal epidermal cells); differentiating intermitotics are the cells more differentiated than the vegetative intermitotics (spermatocytes, myelocytes, oocytes, and spinous cells in epidermis); reverting postmitotics are the differentiated cells that ordinarily do not divide but can under proper stimulation (hepatic cells and renal parenchymal cells); and fixed postmitotic cells are maximally differentiated cells that do not undergo cell division (nerve cells, red cells, and muscle cells).¹

The senescence of cells from the point of view of cytology, histochemistry, and electron microscopy as contrasted to that of cellular pathology is an almost virgin field. The mitochondria of senile cells are reported to be different from those of normal cells as viewed in electron micrographs. More critical analyses of senile cells are required to obtain a firm morphologic basis to understand the aging process.³¹

CONCLUDING THOUGHTS

1. The understanding of the phenomena of growth and development must be based on a complete understanding of the structure and function of an organism at innumerable stages of its life cycle. Total comprehension may come when these stages are linked together in time, the fourth dimension.

2. The complexity of growth and development is obvious. In this context, the investigator is compelled to resolve problems into analyzable units. These manageable units yield much valuable information. The great dilemma of the long-range future is that the ultimate keys to growth and development may be greater than the sum of the analyzable units.

3. Another dilemma is the investigator's judgment to determine the hierarchy of the significance of data. The critical point may be as elusive as deducing the aerodynamics of flight from an examination of the isolated wing of a bird.

4. Form (anatomy) and function (physiology) are in the domain of the anatomist. This should be in the spirit of von Gudden's dictum: "Zuerst also Anatomie und dann Physiologie; wenn aber erst Physiologie, dann nicht ohne Anatomie."

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Contributions of Anatomists to Radiology As Exemplified by the Work of Edward Allen Boyden

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THE CONTRIBUTIONS made by the basic sciences to the clinical branches of medicine are manifold. The first of these is the fundamental knowledge imparted to the medical student from his preclinical courses. This has such an impact upon the future education and practice of the physician that, despite all the experimental changes of the past years, the basic disciplines still retain their vital position in the medical school curriculum. Primary among these disciplines is anatomy. It is the physician's vocabulary, the alphabet of his medical education. It teaches him to understand the structures whose diseases he must eventually treat. While this is true for all physicians, it is especially so for the radiologist. He must be thoroughly familiar with gross and topographical anatomy, with the details of structure. For roentgen diagnosis, after all, is based upon visual anatomy, both normal and pathological. The roentgen ray permits us to extend our vision beyond the surface of the body into its most hidden recesses, to expose the concealed structures in the living individual. But roentgen anatomy is simply an extrapolation of gross and microscopic anatomy, their demonstration in another form. The anatomist is therefore the first and most important teacher of the radiologist; it is the anatomist who gives the radiologist the basic tools which he will use in his future work.

Conversely, roentgenology has a great contribution to make to anatomy. Anatomy can be better taught if roentgen studies are included. In fact, some institutions use the roentgen method in teaching anatomy so extensively that it acts almost as a substitute for various exercises in the delineation of gross anatomical structures. At the University of Oklahoma, for example, Ernst Lachman substitutes roentgen studies for some courses in dissection. The work of Oscar Batson in Philadelphia likewise emphasizes the

possibilities of roentgen examination as a means for the study of anatomy. Nearly all anatomical textbooks today contain numerous roentgen illustrations; some include whole sections on roentgen anatomy.

My own interest in roentgen anatomy dates from my first teaching experience initiated by the late Professor C. M. Jackson. That first elective course was to a section of students in gross anatomy. Using Alban Kohler's "The Borderlines of the Normal and the Pathological in the Roentgenogram" as a guide, I attempted to demonstrate the many anatomical variations which can be seen in roentgenograms of normal persons.

BOYDEN AS PROFESSOR OF ANATOMY

My most extensive contact with anatomy and anatomists, however, began in 1931 when Edward Allen Boyden assumed the professorship of anatomy at the University of Minnesota. We quickly established a cordial working relationship between the Department of Anatomy and the Department of Radiology; it endured throughout his career at the university.

We instituted 2 types of cooperative endeavor. To correlate dissection and anatomical studies with the anatomy of the living individual as exhibited in the roentgenogram, members of the Department of Radiology gave lectures and demonstrations in normal roentgen anatomy to students in gross anatomy. Eventually, graduate students in radiology were used as assistants in anatomical demonstrations. At the same time, the Department of Anatomy offered course work especially suited for the graduate student in radiology, such as topographic anatomy, osteology, and special dissections, all calculated to bring to the graduate student in roentgen diagnosis the more detailed anatomical knowledge which is important to his education. Dr. Boyden worked extremely hard to make this program effective. I am happy to add that this joint endeavor continued under the direction of Dr. Arnold Lazarow after Dr. Boyden's retirement.

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The second significant contribution of anatomists lies in the research field. Not only Dr. Boyden, but many others, such as Oscar Batson, Franklin Huber, and Ernst Lachman, have, through their research, added to the knowledge of the radiologist. But, because I have worked personally with Dr. Boyden, I have chosen to discuss his investigations as an example of what anatomists can contribute to a clinical discipline.

Even fifty years ago, anatomy appeared to many clinicians and, indeed, to many anatomists, a completed science. The physiologist, Walter Cannon, is credited with the words: "Anatomy is a squeezed lemon." Although we counted anatomy as the oldest and the most fundamental of the medical sciences, by the same token we assumed that its votaries had no further new information to offer. In medical histories there appeared the names of the anatomists who, many years ago, drastically changed the course of medical thinking again and again. Today we should not expect such exciting or revolutionary changes, but a competent, enthusiastic investigator may give new life to anatomy. No better illustration of this can be found than in the research of Dr. Edward Allen Boyden.

WORK ON BILIARY TRACT

From the point of view of the radiologist, his studies divide themselves into 2 major areas. The first is in the biliary tract; the second, the respiratory organs. In both of these fields, the contributions of Dr. Boyden have exerted a profound influence on the development of roentgen diagnosis.

Boyden's first published work on the gallbladder dates back to 1922 when he described the pancreatic bladder in the cat and followed this by an intensive study of the anatomy of the cat's gallbladder. In attempting to repeatedly examine the organ in the same physiological state, he hit upon the idea of using the effects of natural foods, particularly fat, on distention of the gallbladder. He fed his animals egg yolk and cream and discovered that the gallbladder could be completely emptied by the stimulus of this meal. The possibility that various foods could be used to influence and study the function of the gallbladder in animals was thus conceived, and he used it to a considerable extent through direct observation.

Evarts Graham visited Boston in 1924 and described his newly devised technic using a contrast material for the roentgen visualization of the gallbladder. Boyden immediately asked his colleagues to use him as a subject for this new procedure. He then took a meal of egg yolk and

cream to determine whether his gallbladder would empty. The experiment proved as successful in the human being as in the cat. The experiment was demonstrated at a meeting of the American Medical Association in Atlantic City in 1925. The method was later described in detail by Whitaker but many of us have always referred to it as the "Boyden meal." From this point he undertook a series of studies of the function of the gallbladder which became of great importance not only to anatomists and physiologists but to radiologists, surgeons, internists, and to anyone who was especially interested in the diagnosis of gallbladder disease.

Dr. Boyden's arrival at the University of Minnesota marked the beginning of a cooperative endeavor with the Radiology Department in his chosen research field. His need for x-ray equipment was pressing. As a result, we put at his disposal the facilities in the X-ray Department of the University Hospitals, at an early hour in the morning, before the routine work of the day commenced. During this time, he carried on one experiment after another on the function of the gallbladder, particularly as it was affected by the use of the egg yolk and cream meal. In this work, Dr. Boyden had the full cooperation of many departments, including obstetrics, pediatrics, medicine, and surgery, as well as radiology. In a long series of experiments, he studied intensively the behavior of the human gallbladder in response to various food substances. Normals ranging in age from the very young to the very old, living under varying circumstances, were studied. He worked out a method of measuring the volume of the gallbladder at various periods after taking the meal. The effects of pregnancy, pernicious anemia, carcinoma of the stomach, peptic ulcer, and other conditions were elucidated. Almost all such studies were pursued with the aid of a staff member or a graduate student of one of the clinical departments, who could make patients available and help interpret the significance of the findings. Many a clinical resident at Minnesota was awakened to the fascination of basic research, as well as to the painstaking care and devotion which it requires, by his association with Dr. Boyden.

Such studies helped to correct many of the misconceptions which had arisen with regard to the tonus of the gallbladder, its contractibility, and its response to a variety of media. The demonstration of changes in the emptying time of the gallbladder as a result of stomach cancer or pregnancy, for example, helped standardize the radiologist's interpretation of the significance of this test of gallbladder function.

In an effort to determine the mechanism of the evacuation of the bile, Boyden, working with a number of his colleagues in radiology, medicine, and surgery, undertook experiments on volunteer medical students with faradic stimulation of the duodenum, at the same time making film examination of the gallbladder to determine its emptying time. The localization of the pain aroused by faradic stimulation considerably influenced our knowledge of gastrointestinal physiology and of the pain centers of the gastrointestinal tract. Boyden was also able to demonstrate that vagotomy did not appreciably influence the time of evacuation of the gallbladder.

Concomitant with these studies, Boyden made detailed dissections of the gallbladder, of its vascular and nerve supply, both in animals and in man. Finally, he described the anomalies of the gallbladder found during these studies of the human cadaver. Some of these were later uncovered in the living individual by means of roentgen examination. In 1935, Dr. Boyden described for the first time the "Phrygian cap" gallbladder, which represented a most important demonstration of the fact that various deformities of the gallbladder, observed roentgenologically, might well be within normal limits. Such observations are of great value to the practice of medicine. There have been times when it seemed that as much harm as good was done by roentgen examination, because of the serious misinterpretations of normal variations which led to unnecessary and often harmful therapeutic procedures. There are many illustrations of such misconceptions, notably the interpretation of epiphysal growth variations as fractures, or of anomalous lobes of the lungs as tuberculosis. It is difficult to determine how many patients were saved operations after Boyden's descriptions of the normal variations of the gallbladder, but certainly prior to that time many such deformities were thought to be due to adhesions and to indicate a pathological state. Aside from its own importance, the designation of the "Phrygian cap" gallbladder as a normal variation had a healthy effect upon radiologists. It made them aware of the fallibility of many other interpretations of roentgenograms of the gallbladder. Radiologists are fully cognizant of the great debt they owe Dr. Boyden, for, without his many studies, their own practical application of the contrast examination of the gallbladder would be far less valuable.

WORK ON ANATOMY OF LUNGS

The second phase of Boyden's work was probably of even greater importance to the roentgen

diagnostician and without doubt it had a profound effect upon surgery and clinical medicine in general. Here he returned to pure anatomy: the physiology which he had utilized so freely in his gallbladder studies was not pertinent to these new investigations of the lungs. In 1945 he began his studies of the bronchial tree and the vascular anatomy of the lungs as related to the pulmonary segments, studies which have occupied most of his research time to the present date. He undertook a careful, detailed dissection of many lungs in an effort to determine the exact distribution of the bronchi, of the arteries and veins, and their numerous variations.

Out of these studies have come the most detailed demonstrations of normal anatomy of the lungs and their deviations, some of which were heretofore unknown, others only partially understood. From the point of view of the roentgen diagnostician these were of first importance for he learned to understand better the great variety of shadows which are visible in roentgenograms of the lungs. Furthermore, at about this time, the use of contrast media for the roentgen visualization of the bronchi came into much more popular esteem. For this reason, the exact pattern of the bronchi became essential.

The terminology of the bronchial tree had never been uniform and, to the student, appeared confusing. The studies of Brock and his associates, Jackson and Huber, and many other investigators served to clarify the terminology. Fortunately for us, Boyden's work gave great impetus to this clarification. He finally proposed a numerical system of designation which was far more useful and more clear-cut than the anatomical labeling which had previously been employed. Here again, the roentgen diagnostician had occasion to be most grateful to Boyden for clearing the air so that the distribution of the bronchi and their relationships to the lung segments as observed in the roentgenogram were standardized.

Boyden's first paper on this subject entitled "The Intrahilar and Related Segmental Anatomy of the Lung," appeared in *Surgery* in 1945. During this time, however, he was studying not only the variations of the bronchial and vascular patterns but some of the gross anomalies, such as agenesis and congenital hypoplasia of the lung, anomalies of the lobes secondary to abnormal vascular development, anomalous pulmonary venous drainage, and many others. His study of bronchogenic cysts and intralobar sequestration clarified ideas in this segment of lung pathology.

Fortunately for radiology and, indeed, for all of medicine, Dr. Boyden's retirement from his posi-

tion as professor of anatomy at the University of Minnesota has not diminished his enthusiasm nor his willingness to continue these investigations of the anatomy of the lungs. In his present position at the University of Washington, Dr. Boyden is pursuing a further detailed investigation of the lung parenchyma which should complement his previous studies of the bronchi and blood vessels.

As radiologists, we owe a real debt of grati-

tude to Dr. Boyden and to the other great anatomists of the present day who have significantly contributed to the effective use of the roentgen ray in the study and diagnosis of disease. The cooperation between anatomy and radiology which is so well exemplified by the work of Edward Allen Boyden must remain as an outstanding example of the benefits which all of medicine can derive from close collaboration of its various disciplines.

PHYSICAL PREPARATION of pediatric patients for operation varies according to individual situations. General procedures include: (1) examination of the child's ears for otitis and of his mouth and throat for obstructing tonsils, pharyngitis, or loose teeth; (2) urine and blood tests, with a hemoglobin level of at least 10 gm. per cent established; (3) restriction of oral intake at midnight; and (4) administration of premedicant drugs, such as atropine, pentobarbital sodium, and morphine, to allay apprehension and decrease undesirable reflexes. The physician should obtain information regarding drug sensitivity, steroid therapy, previous anesthesia experiences, or recent respiratory infection, and the anesthetist should establish personal rapport with the child at a preoperative visit, administer sedative agents, and employ pleasant, nonirritating anesthetic methods in order to achieve undisturbed induction.

Specific preparatory and advisable anesthetization procedures include:

- For hyperexcitable children, preliminary consultation with a pediatrician or psychiatrist; admission to the hospital a day early, perhaps with the mother spending the night in the child's room, to allow for better orientation; and daytime tranquilizers and a sedative at night. Anesthesia: basal, with tribromoethanol (Avertin) or rectal thiopental sodium (Pentothal), before operation.
- For children in poor physical condition requiring elective operations, careful examination for additional defects. Anesthesia: no narcotics and reduced hypnotics, to prevent cardiorespiratory depression.
- For infants, examination for abnormal reflexes and neuromuscular disturbances suggesting lesions of developmental or traumatic origin, congenital cardiac defects, choanal or esophageal atresia, or hyaline membrane disease; establishment of hemoglobin level above 12 gm. per cent; and, to reduce interference with fluid intake, early operation after 2 A.M. feeding. Warmth, oxygenation, and avoidance of unnecessary handling are important. Anesthesia: atropine and vitamin K in place of sedatives.
- For children requiring emergency procedures, sedation and a half-hour calming-down period before operation. Anesthesia: if the child has a full stomach, local anesthesia is preferable; a light anesthetic, such as nitrous oxide, that does not paralyze the gag reflexes is the second choice; if general anesthesia is needed, an endotracheal tube should be passed and kept in place postoperatively until the patient is awake.

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Contributions of Anatomists to Medical Education and Administration

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ANY APPRAISAL of the contributions of anatomists to medical education is difficult to make and must be carefully circumscribed by time limitations and by subject restrictions to avoid that excessive verbalization so dear to the heart of the academician. It would be an easy matter to begin with the history of science and cite those men who, by their labors in anatomy, influenced the course of medicine. One might demonstrate that, were it not for anatomists, medicine and perhaps all of science might well have fallen on evil times or even ceased to exist. Given time and opportunity, physiologists, biochemists, surgeons, pathologists, and internists might contrive to expand the facts to support an identical thesis for their own special fields.

In this country, we are comfortable in our admission that our standards of medical care are the highest, and we lead, while others follow at a respectful distance, in medical education. As teachers of the members of a profession which has achieved this enviable state of perfection, it is high time that anatomists step forward to claim the recognition which is their due.

In doing so, it would be wise not to extend ourselves to the degree ascribed to one of our former colleagues. The story goes that the anatomist delegate to a curriculum committee was reporting back to a departmental conference. He was explaining the difficulties of getting a medical faculty to agree to loosen their several strangleholds on teaching time in order that revisions might be made and new material included. The trouble seemed to be that the proponent of each discipline was sure that his was the most important subject for the medical student. The biochemist was certain that, if the student really understood his subject, he could comprehend the nature of disease, for after all, sickness is nothing but the result of disordered body chemistry. The physiologist was equally confident that,

since disease is caused by anomalous physiology, only a thorough understanding of the normal would permit the budding physician to be aware of the abnormal. The pathologist, not to be outdone, was forthright in his statements that it had long been known that illnesses occur because of abnormal anatomic situations; therefore, how could a student be expected to grasp the fundamentals of disease without a complete grounding in pathology? The microbiologist, secure in his belief that external agents can cause body disorder, was sure that comprehension of his discipline must not be denied the future clinician.

One of the older members of the department obviously grew more restive by the moment during this recital of virtues and necessities. When he could no longer contain himself, he demanded to know what was wrong with such a pack of dolts—didn't they know that anatomy was the queen of the medical sciences and that no man could hope to become a good physician without a complete knowledge of human structure?

THE HISTORICAL BACKGROUND

This directness of approach is certainly commendable, even if not a prime example of reticence. Anatomists have always had much influence on medical education; indeed, at times they and the discipline they taught *were* organized medical education. This rich tradition ranges through Aristotle, Marinus, Galen, Avicenna, Mondinus, Leonardo da Vinci, Vesalius, Harvey, Hunter, the Munros, Cadwalader, and Shippen and Morgan. Historically, their investigations laid the foundations for much of medical science, and their contributions are presently continuing to influence research trends. The broad view taken by adherents of our science early in the century has certainly been one of the most potent factors in medical education in our times.

Perhaps the greatest contribution that the early anatomists made to medical education was the break from the stifling tradition of anatomy for

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the sake of its practical utility in medicine. The younger ones began to insist that the experimental methods of biology be directed toward the scientific understanding of form. From these primitive beginnings came a steady stream of men and ideas that broadened the concepts of medicine generally and introduced into the medical curriculum much of what is now known as scientific medicine. Anatomy cannot claim sole credit for this revolution in medical teaching, for physiology, physiologic chemistry, and microbiology were also burgeoning sciences. However, anatomists have never felt hemmed in by disciplinary boundaries in either their selection of or their attack upon biologic problems. When rigid lines of departmental discipline needed to be crossed, there appeared an anatomist who did not hesitate to become competent in the allied field in order to aid him in the solution of a problem.

In 1961, no eyebrow is lifted when interdisciplinary attacks on biologic problems are made. It is the order of the day for the surgeon to study the transport of sodium in the small intestine; the internist to concern himself with scintillation scanning of the spleen; the pathologist to write of antidiuretic hormone and water absorption in the colon; and a team comprised of mathematician, pathologist, surgeon, and internist to examine the bronchial epithelium in former cigaret smokers.

Scammon and his associates did not find this kind of acceptance, and therefore scientific respectability was not easy to come by when their quantitative studies of human growth were begun. Harrison and his students in experimental embryology, who contributed many men and great ideas to medicine, were looked upon as being a little out of the ordinary. Bensley became a more-than-acceptable chemist to get at the mysteries of cellular organization, and Jackson did not hesitate to break into the new field of nutrition, for there he saw the tools which might help explain form. Downey became an expert in some phases of clinical hematology because of his interests in form changes in blood cells. These are but a few of those who broke away from the traditions of strict descriptive morphology and whose work has had a profound effect on the course of medicine and biology. The list is long and should be a source of great pride to the adherents of anatomy.

COOPERATION OF DISCIPLINES

The introduction of all disciplines into the mysteries of form has made an impact on medical education which, it is to be hoped, will last.

Perhaps the greatest single thing it has accomplished has been the almost complete disruption of the trade-union concept of teaching in medical schools. No longer does any department feel constrained to restrict its use of knowledge in a teaching program. If function will help to explain form or if form will aid in making clear a function, no one hesitates to use the facts and materials necessary to the issue. Cross-disciplinary appointments are made in most of our medical schools, and these will become even more prevalent as men and their talents continue to range freely in research and teaching. It is not unusual for the neuroanatomist to teach neurophysiology and even neurochemistry. Clinicians of all descriptions are adept in some basic science.

It is difficult to overestimate the importance of this one contribution to medical education. Medicine, because of the economic implications of practice, has tended to box in its medical school departments. All too frequently, teaching has been governed by medical economics rather than by that which is rational or educationally sound.

It would be highly agreeable if anatomists could take the full credit for this collapse of disciplinary boundaries in research and in teaching, but to do so would put us in a position which is difficult to sustain. It can be said with assurance that anatomists took the lead in branching into those areas which many of our more conventional colleagues felt were not in our province. This daring on the part of a few added greatly to our knowledge and has done much to strengthen the position of anatomy in the medical curriculum. It has made it possible for anatomists to continue to be vital members of the medical community, because they are important contributors to all phases of the advance in knowledge of human biology.

ANATOMISTS AND ADMINISTRATION

The assessment of the influences of anatomists in medical education can be done with some precision, for the beginning of trends can be spotted with reasonable accuracy. The effect that anatomists have had on the administration of medical schools and their appurtenances, the hospitals, is more difficult to determine. Here it is not enough that a dean or some other official had his beginning as an anatomist. This precious heritage is no proof of the salubrious effect of his administration.

It probably can be demonstrated that about as many anatomists have made good deans as have made bad ones. Interesting in this connection is the fact that so many medical school

deans are anatomists. An incomplete study of this social phenomenon reveals that more than 20 of our medical schools have had anatomists as deans since 1930. In the same time span, anatomy spawned 7 associate and 9 assistant deans, 3 deans of university divisions of biologic sciences, 3 deans of graduate schools, 11 directors of institutes of medical sciences or categorical disease study, 2 vice-presidents or vice-chancellors of universities, 5 presidents or heads of university medical centers, 3 presidents or vice-presidents of the Association of American Medical Colleges, and at least 2 chiefs of divisions of the National Institutes of Health. These data are certainly incomplete and can only be made wholly accurate by a study of the complete *curriculum vitae* of all anatomists of this era.

It might be enough to say that the people who were drawn from the ranks of anatomy kept the institutions or segments thereof for which they were responsible in reasonably good working order. This in itself would be a considerable contribution and even in some cases might be true. A more careful study than this can ever

pretend to be must show that many medical schools and their allied institutions have developed because of wise and devoted administrators who learned the importance of being humane and understanding while serving as investigators and teachers in the broad fields of anatomy. They also must have learned that decisions have to be made and that all personal ambitions of every member of an institution cannot be satisfied.

Space does not permit the full development of the many influences that anatomists have had on medical education. They have, from the beginning of scientific history, had sufficient strength to insure their place in the sun. The record of their activities and the current responsibilities they shoulder should provide them with assurance. Medicine and the schools which teach it have always needed the special knowledge and the guidance which the anatomist alone can provide. Two thousand years of this should demonstrate that minor fluctuations in our fortunes are to be expected and may well be the cause of concern but these should not be allowed to become the cause of fear.

RATE of physiologic disposition of ingested steroids in rats is more important than absorption rate in determining peak blood levels and pharmacologic potency. Rate of absorption from the small intestine can be predicted from the structural formula of steroids: the more lipoidal the compound, the greater the absorption rate; the more polar and water soluble the agent, the slower the absorption rate. In general, absorption varies inversely with oxygenation, and the hydroxyl group is more effective in inhibiting absorption than the carbonyl group. Percentage of absorption is independent of concentration, suggesting that steroids are absorbed from the intestine by diffusion. Compounds such as testosterone, progesterone, and deoxycorticosterone are absorbed most rapidly, but oral as compared with parenteral potency is weak. By contrast, triamcinolone, dexamethasone, and prednisolone are extremely potent when given orally but are poorly absorbed. Cortisone has the lowest plasma levels despite the fastest rate of absorption.

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Contributions of Anatomists to Internal Medicine

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*"All work is as seed sown; it grows and spreads,
and sows itself anew."*

THOMAS CARLYLE:
On Boswell's Life of Johnson

THE BLUE and yellow threads of many disciplines are expertly blended to produce the finished green hood symbolic of medicine and the healing arts. Indeed, it is quite impossible to grasp a dominant thread in the cloak of Aesculapius and identify it as the sole contribution of any one basic or clinical science. It has been said that anatomy is to physiology, pathology, physical diagnosis, and surgery as geography is to history—namely, it provides a setting for the events. The scientific interrelationships between biological chemistry, microbiology, pharmacology, and internal medicine are recognized by all, whereas anatomic contributions to medicine per se are less apparent and often obscure. To the inexperienced or casual observer, the significance of structural contributions is often lost—much as the canvas of a completed painting becomes hidden beneath overlapping brush strokes and layers of blended color.

To enumerate the specific contributions of individual anatomists to internal medicine, let alone each of the medical specialties, would be imprudent. Indeed, within the limited scope of this paper, it is impossible to state where pure anatomical work ceased and the influence of the internist began, for many renowned personages could be claimed equally by either of these medical sciences.

One area of vital concern to every internist and anatomist is that amazing organ, the heart. This efficient muscular pump affords a unique example of the interplay between several disciplines. It is true that Franklin P. Mall, E. N. Walls, B. M. Patten, and many other anatomists have added to the basic knowledge of the em-

bryology and structure of the heart. In a similar way, our appreciation of the nerve supply of this intricate organ was measurably enhanced by the superb works of Ramon y Cajal and José F. Nodde. However, the greatest of fundamental contributions to our knowledge of the heart were made by practicing physicians who had maintained a lifelong interest in structure due to their earlier training in anatomical dissection or the actual teaching of anatomy. For example, Giovanni Morgagni was trained in philosophy as well as medicine and was appointed to the chair of anatomy at Padua, formerly occupied by such stellar anatomists as Vesalius, Fallopius, Caserius, and Spigelius. Morgagni was a favorite with both his students and colleagues throughout his long life and is known to all present-day students. His famous book, *De sedibus et causis morborum*, founded the science of pathological anatomy; described cerebral gumata, mitral disease, aneurysms, acute yellow atrophy of the liver, and tuberculosis of the kidney; and gave the first clear account of heart block. Perhaps the best remembered and most quoted words of this celebrated physician are:

Those who have dissected or inspected many bodies, have at least learned to doubt; when others, who are ignorant of anatomy and do not take the trouble to attend to it, are in no doubt at all.

The equally eminent physician-anatomist, John Hunter, was not only a skilled dissector and inveterate experimenter but an author—his writings on angina pectoris, gunshot wounds, inflammations, pyemia, and shock have become medical classics. His inquiring mind helped forge the evolving sciences of experimental and surgical pathology. He also found time to engage in, among other things, studies of digestion during hibernation in lizards and snakes and investigations of hearing in the fish. Indeed, he made his own opportunities and, in so doing, made medicine great.

To the list of illustrious physicians, one could add the all-important contributions to cardiac

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knowledge of Arthur Keith and Martin Flack, who discovered the sinoatrial node; Tawara, the Japanese physician who so beautifully described the atrioventricular node; John B. MacCallum, who ingeniously unrolled the heart to demonstrate its muscle layers; Adam Thebesius, who injected a variety of materials into the coronary veins to demonstrate their endocardial ostia; and Jan Swammerdam, whose productivity in forty-two short years was incredible. He identified red blood cells and devised microdissection devices of great intricacy for his experimental work, including injection syringes and a simple plethysmograph for measuring the volume of the heart in systole and diastole.

Functional interrelationships between the circulation and respiration are obvious and well known to every first-year medical student. The pioneering anatomic studies of William S. Miller, Chevalier Jackson, Sr., and J. Franklin Huber, and Heinrich von Hayek on the lobulation and pulmonary segmentation of the lungs, are included in all standard anatomy and clinical textbooks. The significant observations of lung structure with the light microscope by A. Kölliker, W. von Möllendorff, C. C. MacKlin, and C. G. Loosli are rivaled only by the recent electron microscopic studies of Frank N. Low. The detailed branching and segmentation of the pulmonary vessels were beautifully portrayed in the several papers of Edward A. Boyden and serve as valued anatomic landmarks for modern thoracic surgery. It is appropriate to note that Dr. Boyden's work was completed at the University of Minnesota, the institution being honored in this special issue of *The Journal-Lancet*.

The literature on the lung, as that of the heart, is profusely documented by the magnificent contributions of many prominent anatomists-physicians. We usually associate the name of Thomas Willis with that of the arterial circle on the basilar surface of the brain, yet his major contributions to medicine probably were his lucid descriptions of asthma and pleurisy.

The anatomic contributions to the heart and lung literature mentioned here are admittedly selected and incomplete. They only scratch a small area of the visceral domain that falls within the province of internal medicine. Valuable anatomic studies on the gastrointestinal, reproductive, and excretory systems could have been cited instead. All these contributions were pertinent and often had practical applications in more than one clinical field. From each course of cognate anatomy—that is, embryology, histology, neuroanatomy, and systemic gross anatomy—one could illuminate and follow threads of in-

formation that are daily unlocking medical mysteries and providing norms for diagnoses and rational therapy. Such basic facts are indeed woven into the mental fabric of every physician. Yet research is far from being the sole anatomic contribution to medicine. Two additional presentations merit brief consideration.

The first of these endowments lies in the wealth of precise research methods of anatomy which have been applied so successfully in the clinical sciences. These embrace a wide variety of techniques that range from the histochemistry and electron microscopy of cellular detail to a battery of more gross methods. Most of them are aimed at the identification of normal and pathologic tissue; other methods provide qualitative structural answers after experimental procedures. Research results are only as reliable as the limitations of the methods employed, and in the realm of cellular and tissue techniques, the anatomist has indeed made a memorable contribution to science. A counterpart of methods, and of equal importance, is the wealth of excellent anatomic textbooks and illustrations. These ancillary teaching arms of anatomy have had an influence upon the knowledge of the medical student which is probably unparalleled in the medical sciences. Who among us could determine the limits of influence of, or the numbers of physicians that have been influenced by, the skilled editorial labors of such deceased anatomists as Andreas Vesalius, Henry Gray, Clarence Jackson, J. P. McMurrich, Johannes Sobotta, Werner Spalteholz, and their modern counterparts?

The second additional aspect, and perhaps the most important contribution of all to internal medicine, is the fortuitous role of the anatomist in igniting the spark of curiosity of the medical student during the most receptive period of his training. The first pair of molding hands is usually that of the anatomist. The annals of medical history are replete with examples of famous physicians who were successfully launched on the road to medicine by the kindling spark of anatomy.¹⁻³

The author admits to a thorough and enjoyable perusal of the fascinating book by W. C. Gibson⁴ entitled *Young Endeavor*. This inspiring volume places particular emphasis upon the remarkable discoveries that were made by young medical students and might well be placed on the obligatory reading list for both medical students and faculty. Gibson has likened the medical student to a seed, the university atmosphere to the soil, and the medical faculty to the weather and nourishment. All three factors are es-

essential to the maturation of either a strong plant or a competent physician.

The opening lines of Carlyle recall the following appropriate words of Rufus Jones:⁵

Nobody knows how the kindling flame of life and power leaps from one life to another. What is the magic quality in a person which instantly awakens faith? You listen to a hundred persons unmoved and unchanged: you hear a few quiet words from the man with the kindling torch and you suddenly discover what life means for you forevermore and you become forthwith another man, carrying perhaps your own torch.

What kindly words, imaginative questions, or nourishing environments made possible the continuous rich harvests from the fruits of Vesalius to his pupil Fallopius, who taught Fabricius, who, in turn, taught William Harvey? It is certain that a spark of inquiry passed from an anatomist interested in physiology to a physiologist who finally made sense of the anatomy of the heart and circulation. We can only surmise the influence that the immortal John Hunter had upon his pupils Edward Jenner, of vaccination fame, and the distinguished surgeons Abernathy, Cline, and Astley Cooper. Was it the soil or the nourishment that attracted Lister, Huxley, and James Blake to William Sharpey's laboratory or Virchow, Remak, Helmholtz, and Gruby to the laboratory of Johannes Müller? Did the kindling

spark of the anatomist, Philip Magnus, ignite the imagination of Sir Victor Horsley, and he in turn light the torch of the beloved Thomas Lewis? What were the encouraging words of Koster, the anatomist, to young Willem Einthoven as he patiently pursued the mechanics of the elbow joint—for he became, not an anatomist, but the father of electrocardiography?

Who is to say which disciplinary thread is brightest or strongest in the cloak of Accusapius? In the whole cloth of modern medical education, the multicolored research threads of many sciences, as well as the philosophy of innumerable faculty members, must be expertly woven to provide a stimulating diet for the growing mind of the medical student.

The anatomists can look with justifiable pride upon their particular contributions to the training of a competent physician, for as this seedling grows and spreads new seed, so the anatomists' labors will provide nourishment to generations yet unborn.

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PATIENTS with hyperglycemia but without overt gastrointestinal symptoms may have insufficiency of pancreatic exocrine secretion, as determined by radioiodine-labeled fat absorption tests. Of 20 such patients, 4 had secretory deficiency and 1 had borderline dysfunction, judged by abnormal triolein but normal oleic acid absorption, diabetic type of hyperglycemia, and correction of the triolein absorptive defect by oral administration of pancreatin. All 5 had more than one bowel movement a day and 1 had gross steatorrhea; 4 of the subjects drank alcohol habitually, 3 to excess.

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The Fourth Dimension of Anatomy

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I. Present-Day Research

ANATOMY, like physics, has its fourth dimension—time. Time, itself, has contributed to this evolution through the pursuit of new knowledge and new approaches to technic and laboratory equipment. The early anatomists were concerned with the static aspects of structure; present-day anatomists are more concerned with the dynamic aspects—that is, how structure varies with time in the process of ordinary physiologic change, as well as under experimental conditions. Although some may consider this physiology or biochemistry, it is “modern” anatomy.

In seeking to understand the body, the anatomist has proceeded from the organs to their cells, to the characteristics of subcellular components (organelles) and ultimately to the actual localization of individual molecules within these organelles. Van Leeuwenhoek, in the seventeenth century, actually started this evolution. His microscope and the subsequent improved design of conventional light microscopes opened the way for more detailed cytologic study. With the advance of the electron microscope, whose magnification permits the resolution of the larger protein molecules, our greatest expectations have been surpassed.

By contrast, the biochemist started with a study of the structure of individual molecules and the reactions between them. Ultimately, however, in order to understand the living process, it became necessary for him to localize these molecules and their reactions within the organelles of the cell. Although the methods and instruments of the biochemist and the anatomist have differed, both are concerned with the same problems and often employ similar techniques. Thus we see that there is no major line of demarcation between these fields; the biochemist starts at one end of the spectrum, so to speak, and the anatomist starts at the other.

New developments during the past several decades have provided new instruments and

technics for studying the fourth dimension of anatomy. These include: the phase, interference, ultraviolet, polarizing, and electron microscopes; tissue culture; mierodissection; cell fractionation; and histochemical and radioautographic techniques.

STUDY OF LIVING CELLS

When examining a living cell under the ordinary microscope, only a minimum of cytologic detail can be seen. Stained preparations may be used to bring out more details; however, these preparative procedures may produce artifacts.

Recent advances in optical techniques have led to the development of the phase microscope, interference microscope, and the ultraviolet microscope. These new instruments have permitted more detailed observations of the living cell at high magnification.

Within the living cell one can see many organelles, follow cell movements, and study the movement of mitochondria within the cytoplasm of cells. During cell division one can see the individual chromosomes line up, divide longitudinally, and separate.

The development of the quartz-rod-transillumination technic has made it possible to examine living tissues within organs. Using this method, one can observe the flow of blood through the capillaries of the liver, the response of the small blood vessels to specific drugs, and the phagocytosis of particulate matter by the liver sinusoidal cells.

TISSUE AND ORGAN CULTURE

Tissue and organ culture provide methods whereby cells or organs can be grown outside the body. When proper nutrients are present, the cells may continue to grow for prolonged periods; often they maintain their specialized structure and properties. Factors influencing cell growth and differentiation can be evaluated in tissue culture. Utilizing these methods, the synthesis of hormones outside the body looms as a very productive goal in research.

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NATURE'S WISDOM IN PROVIDING ANIMALS FOR EXPERIMENTATION

Nature has been provident in her anatomic wisdom by arranging the structure of certain animals in such a way that they become ideal subjects for specific biologic experimentation. For example, the islet tissue in certain fish is separate from the acinar pancreas; the insulin-producing cells are thus concentrated into a discrete body designated as the principal islet. This anatomic variation contrasts with mammalian species where the 1,000,000 individual islets are scattered throughout the pancreas. Thus fish (*Lophius piscatorius*, in this instance) provide quantities of islet tissue which may be used for the study of insulin synthesis.

Likewise, the Japanese Medaka (*Oryzias latipes*) is particularly well suited for studying factors influencing embryologic development because the female of this species very conveniently lays eggs on her tail fin each morning. These may be collected, fertilized, and subjected to experimental condition; with a supply at hand, one can study the factors which produce developmental anomalies.

It does seem provident that fish, far removed from man on the evolutionary ladder, are providing significant information for the understanding of human diabetes and embryologic development.

MICROMANIPULATION AND DISSECTION OF CELLS AND TISSUE COMPONENTS

Micromanipulative procedures have been developed which make it possible to work on individual living cells; microinjections may be made within the cytoplasm of the cell or the nucleus may be surgically removed. Using frozen dried tissue sections, one can microdissect groups of cells, individual cells, or parts of single cells under the binocular dissecting microscope; these are accurately weighted using a quartz-fiber microbalance. Samples of tissue weighing less than 0.100 μ g. have been analyzed for their chemical composition and enzymatic properties. The component layers of the retina have been dissected, individual nerve cells separated and analyzed, individual islets of Langerhans have been obtained from the rat pancreas, and their insulin content determined.

ELECTRON MICROSCOPE AND THE ULTRA- STRUCTURE OF THE CELL

Probably the first electron microscope used in the United States was built by an anatomist who is also a Minnesota graduate. Utilizing detailed

information on design and construction of electron microscopes published in the German literature, Gordon H. Scott built an emission-type microscope, actually winding the magnetic lenses with his own hands.

With the emission-type microscope, the tissue sections are placed on the cathode and heated to varying temperatures; at specific temperatures, certain elements will emit electrons. These are then focused by the magnetic lenses of the microscope and an image is obtained of the component within the cell which was the emitting source. By this method, the localization of calcium plus magnesium within cells was contrasted with that of sodium plus potassium.

The electron microscopes in use today operate on a principle similar to that of the light microscope, except that a beam of electrons is used in place of light. This electron beam is passed through the tissue section which absorbs or scatters electrons; magnification is accomplished by means of an electromagnetic field (lenses), and an image is projected on a fluorescent screen or photographic plate.

Although the electron microscope has great resolving power, its use is limited to sections of tissue that are approximately 0.02 μ thick; the electron beam will not penetrate thicker sections. Another minor complication is that the tissues must be examined in a vacuum and therefore must be dried before study. Special methods for imbedding tissue had to be developed; the best knives for cutting such thin sections are made of glass which has been broken in a special way to provide an appropriate cutting edge.

Electron microscopes became commercially available in the early 1940s, and today there is hardly a department of anatomy in this country which does not have one or more of these instruments.

With the increased resolving power of the electron microscope, new concepts of the ultrastructure of the cell have emerged. Mitochondria, for example, long recognized as "rod-shaped or spherical organelles" are now known to be complex structures. They are bounded by a double membrane, the inner layer of which projects into the interior, forming a series of cristae. The internal fluid compartment within the mitochondria appears to be separate from that of the cytoplasmic intracellular fluid. The basophilic region of the cytoplasm containing the so-called chromophil substance has been shown to consist of an aggregation of flattened membranous sacs which are associated with numerous spherical particles applied to the outer surface. These particles, called ribosomes, con-

tain ribonucleic acid (RNA) and they measure about 200 Å (angstrom units) in diameter.

The multitude of problems that can be studied to advantage with the electron microscope is so great that cytologists, histologists, pathologists, and experimental biologists will be kept busy for many decades to come.

CELL FRACTIONATION

The ability to separate the component parts of the cell presents many interesting possibilities for research. The separation of mitochondria in 1934 heralded a new era in cytochemistry.

Cell fractionation is performed after the cell membranes are broken; this was originally accomplished by squeezing the tissue through bolting silk, more recently by gently grinding the cells in a glass homogenizer. The organelles of the cell are thus liberated into the suspending media, and they can be identified under the microscope. The suspension is centrifuged successively at various speeds and for various lengths of time to separate the cell components. Appropriate quantities of nuclei, mitochondria, and endoplasmic reticulum can be obtained for study. Conventional analytic and biochemical methods can then be used to determine the chemical constitution and enzymatic properties of each cell constituent. Fractionation of cell components has become a common procedure used by the anatomist and biochemist alike.

Utilizing this procedure, mitochondria, for example, are found to be active metabolic sites within the cytoplasm where many of the respiratory enzymes and enzymes for fatty acid synthesis are concentrated. We might think of mitochondria as power plants where basic chemical reactions take place and where high-energy intermediates such as adenosine triphosphate (ATP) are formed.

The microsome fraction, which corresponds to the endoplasmic reticulum as seen under the electron microscope, is concerned with the synthesis of proteins. The ribonucleic acid (RNA) component of the microsome is intimately involved in the formation of the newly synthesized protein molecule. Present concepts suggest that the gene, believed to be represented by a deoxyribonucleic acid (DNA) component in the nucleus, serves as a template which forms a secondary RNA template. The latter is ultimately transferred to the cytoplasm where it serves as a template for protein formation.

HISTOCHEMISTRY

Histochemistry is concerned with the localization of specific chemical constituents and

enzymes within individual cells or within component parts of the cell. Localization of the different types of nucleic acid, proteins, and carbohydrates has been made. Histochemical sites of enzymes have been identified by visualizing an insoluble product which has been formed as a consequence of a specific enzymatic reaction. The reaction-product is converted to a colored derivative by coupling to dyes and may then be seen under the microscope within individual cells and, in some instances, within subcellular structures such as mitochondria. Adaptations of histochemical techniques are being made for use with ultrathin sections which can then be studied under the electron microscope. This new phase of histochemistry offers great promise.

RADIOAUTOGRAPHY

Radioautography is a technique whereby the site of radioactive compounds within cells may be visualized. Although compounds containing tritium, an isotope of hydrogen, have been found particularly advantageous, many different isotopes have been used. When tritium-labeled isotopic compounds or precursors are administered, they may be selectively incorporated into specific chemical compounds within certain cells or organelles.

In order to visualize the contained radioactive compound, a thin layer of photographic emulsion is placed on the surface of the tissue section. When the radioisotopes disintegrate, the released beta particles activate the silver grains in the emulsion. When the beta particle is of low energy, as is the case with tritium, it travels a limited distance only and, therefore, the activated silver grains are limited to the proximity of the radioactive sites. Subsequent photographic development reveals a black silver deposit immediately overlying the radioactive site. The amount of radioactive compound can be estimated by counting the number of individual silver grains visible per unit area of tissue section.

By comparing the number and distribution of silver grains within the underlying stained structures one can show, for example, that tritium-labeled thymidine is incorporated into the deoxyribonucleic acid (DNA) of the nucleus during a limited period immediately preceding cell division but it is not incorporated into the DNA of a resting nucleus or into the ribonucleic acid (RNA) of the cytoplasm.

Improvements in radioautographic technique have permitted localization of radioactive compounds at the electron microscope level. When tritium-labeled amino acids are administered, they are incorporated into specific proteins. In

the pancreatic acinar cell, for example, it is possible to identify radioactivity in the region of the endoplasmic reticulum within a few minutes after administration of the isotope. Shortly thereafter, it appears to be concentrated in the Golgi area of the cytoplasm, and subsequently it is found within the secretion granules.

SUMMARY

In contrast to the concept held by many, that an anatomist is one who works on bones and cadavers, the modern anatomist uses a variety of new research approaches. These include: the

phase, interference, ultraviolet, polarizing, and electron microscopes; tissue culture; microdissection; cell fractionation; and histochemical and radioautographic techniques. Because of these, the science of anatomy is developing more rapidly than at any time in its history. Anatomy provides a rich opportunity for individuals with varied aptitudes and training who are interested in a multidisciplinary approach to the study of structure and to the changes in structure with the passage of time.

To study thus is to study anatomy in its fourth dimension.

II. Graduate Training in Anatomy: Past, Present, and Future

DURING the past half century, the Department of Anatomy at the University of Minnesota has served as a major training center for anatomists. A significant number of those receiving postgraduate training have brought honor to this university through their professional accomplishments. Although a majority of those attaining the Ph.D. degree have held positions in anatomy departments in medical schools, others have gone into related fields. Some have assumed administrative responsibilities, including those of a medical school deanship and chancellor of a university. A number of graduates have also earned the M.D. degree; some have become distinguished leaders in clinical fields such as neurosurgery, pediatrics, and obstetrics.

The universities of Minnesota, Michigan, and Chicago are the only three in this country that have trained more than 50 anatomists during the thirty-five-year period, 1924 to 1959.¹ During the five-year period between 1951 and 1955, Minnesota granted 13 Ph.D. degrees in anatomy, while only 136 were awarded for the United States as a whole.² A total of 72 Ph.D. degrees in anatomy have been awarded at this university since 1913.

The number of master's degrees granted during this period correlates closely with the Ph.D. record. In addition to the 26 students who received both a master's and a Ph.D. degree from this department, 72 received either an M.A. or M.S. degree, and a significant number have gone on to complete their medical training.

SHORTAGE OF ANATOMISTS

There is a national shortage of trained personnel in all the basic medical sciences and anatomy

is no exception. According to a recent survey conducted by the American Medical Association, 52 budgeted full-time faculty vacancies existed in anatomy departments of medical schools in the United States in the 1960-61 academic year.³ During the past four years, an average of 28 Ph.D.s in anatomy have been granted each year by all of the graduate schools in the United States.

Assuming that there is a total of 900 budgeted positions in anatomy among the medical schools in this country and that, on an average, each individual will devote thirty years to the pursuit of his career, it would be necessary to turn out 30 new Ph.D.s each year simply to replace those anatomists who are lost through retirement or death.

Furthermore, at least 20 new medical schools are needed during the next ten years in order to provide sufficient physicians for our growing population. If we project the staff needs on a basis of 10 anatomists for each new medical school, 200 more anatomists will be necessary. In addition, anatomists are also in demand for a variety of research projects in various related fields.

Nor can we ignore the fact that many anatomists enter collateral fields to make important contributions, particularly in clinical research and teaching. However, these individuals are lost to the basic science departments.

Thus, we have not graduated sufficient anatomists over the past few years to fill the vacancies that exist, let alone fill unbudgeted positions, to staff new medical schools, and to provide research personnel for expanding medical research projects.

DEPARTMENT OF ANATOMY STAFF

University of Minnesota 1961-1962

INSTRUCTIONAL ACADEMIC STAFF

Professors

Lazarow, Arnold, M.D., Ph.D. (head of department)
Hartmann, J. Francis, Ph.D.
Morgan, Charles F., Ph.D.
Sundberg, R. Dorothy, M.D., Ph.D.
Wells, Lemuel J., Ph.D.

Associate professors

Carpenter, Anna-Mary, M.D., Ph.D.
Felts, William J. L., Ph.D.

Assistant professors

Hally, A. Douglas, M.D. (visiting professor)
Heggstad, Carl B., M.D., Ph.D.
Smithberg, Morris, Ph.D.

Instructors

Buckman, Mary Jane, Ph.D.
Thorsell, Walter K. (mortuary science)

EMERITUS STATUS

Boyden, E. A., Ph.D., *professor*
Miller, Shirley P., Ph.D., *assistant professor*

RESEARCH ACADEMIC STAFF

Brekhus, Elmo, research associate (documentation)
Dixit, Padmakar K., Ph.D., research associate (biochemist)
Hoiland, Lucille J., M.D., research associate
Jedlicka, Philip A., research fellow (electrical engineer)
Lowe, Irene P., Ph.D., research fellow (microchemist)
Morgan, Carl R., research fellow
Speidel, Edna A., Ph.D., research fellow (biochemist)

GRADUATE STUDENTS

Dental trainees (Ph.D. candidates)

Isaacson, Robert J., D.D.S.
Mundt, Robert, D.D.S.
Stallard, Richard E., D.D.S.

Combined M.D.-Ph.D. candidates

Carlson, Bruce M.
Lindall, Arnold W.
Papermaster, Benjamin W.
Wright, David L.

U.S.P.H.S. trainees and teaching assistants (Ph.D. candidates)

Bauer, G. Eric
Honour, John H.

Kvistberg, David R. (biochemistry and anatomy)
Mathews, Robert J.
Morehead, James R.
Murrell, Leonard R.
Neukirch, Lois M.
Rausch, Verna
Rigatuso, Joseph L.
Robertson, Donald W.
Sacconan, Frank
Schweisthal, Michael R.
Seale, Raymond U.
Stenerwald, Erla A.
Traurig, Harold H.
Whitmore, Mary R.
Yoshihara, Henry

Master's degree candidates

Blum, Beverly L.
Swency, Laura

TECHNICAL STAFF

Anderson, Marion J., junior scientist
Andre, Harry P., principal laboratory attendant
Baker, Jovita, junior scientist
Crews, Paul, principal laboratory animal attendant
Deyo, Rita C., senior laboratory technician
Dunigan, Claudia J., laboratory technologist
Fishbaugh, William D., laboratory technologist
Herbst, Gordon H., junior scientist
Holmberg, Henry A., senior animal laboratory attendant
Kickert, Virginia R., laboratory technician
Kronstedt, Loris Ann, senior laboratory technician
Lear, Margery H., laboratory attendant
Lewis, Virginia A., senior laboratory technician
Lindsey, Charlotte, laboratory technician
Lothe, Ruth, laboratory technician
McRoberts, Janet K., laboratory technician
Marhenka, Randa, junior scientist
Matheny, Marilyn T., laboratory technician
Mottaz, Lenore E., laboratory technologist
Ogrins, Skaidra A., senior laboratory technician
Patterson, Letha L., laboratory technologist
Uittenbogaard, Bernice M., senior laboratory technician
Whitley, Janet L., laboratory technologist
Winfield, Maxine W., laboratory technologist

SECRETARIAL STAFF

Adams, Margery P., editorial assistant
Carter, Lois M., principal secretary
Connors, Vera M., senior accounting clerk
Diethelm, Elizabeth Q., senior clerk typist

FEDERAL RECOGNITION OF NEED
FOR BASIC SCIENTISTS

The Federal Government became concerned with the severe shortage of trained personnel in all the basic medical sciences, and in 1958 the National Institutes of Health took an important step by providing training grants. The Department of Anatomy at the University of Minnesota was fortunate in obtaining an anatomical sciences training grant in September 1958—one of the first training grants awarded in anatomy.

Under this program, a graduate student receives a stipend beginning at \$2,600 for the first year and increasing to \$3,300 in his final year. All tuition fees are paid and allowances are made for dependent children: \$500 for the first child and \$350 for each additional child. With this program, the number of graduate students has increased markedly, both at Minnesota and in the country as a whole.

Twenty-six students are now enrolled in graduate study in the Department of Anatomy at the University of Minnesota: 17 are candidates for the Ph.D. degree, 4 are working toward a combined M.D.-Ph.D. degree, 3 are graduate dentists working for a Ph.D. in anatomy, and 2 are enrolled as master's candidates.

This graduate training grant permits students with high ability, but who are without sufficient financial backing, to complete graduate training which otherwise would be impossible. Physicians have a special vantage point for identifying these gifted young people and encouraging them to seek careers in the basic medical sciences.

REFERENCES

1. ELDRED, E., and ELDRED, B.: Supply and demand for faculty in anatomy. *J. Med. Educ.* 36:134, 1961.
2. Association of American Medical Colleges: The Teaching of Anatomy and Anthropology in Medical Education. Report of the Third Teaching Institute, Swampscott, Massachusetts, October 18-22, 1955. Chicago: Neeley Printing Co., 1956, p. 87.
3. Medical Education. *J.A.M.A.* 178:591, 1961.

PH.D. DEGREES GRANTED
Department of Anatomy, University of Minnesota
1888 through December 1961

<i>Date</i>	<i>Name (Faculty advisor)</i>	<i>Title of thesis</i>	<i>Most recent position</i>
1915	WILLIAM FITCH ALLEN (J. B. Johnston)	The Spinal Cord of <i>Bdellostoma</i>	Prof. and head, Dept. of Anatomy, Univ. of Oregon. Deceased 1951
	EDWIN A. BAUMGARTNER (R. E. Scammon)	Development of the Liver, Gall Bladder and Hepatic Ducts in <i>Amblystoma punctatum</i>	Pathologist, Newark State School, Newark, New York. Deceased 1942
1916	ELMER RAY HOSKINS (C. M. Jackson)	The Growth of the Body and Organs of the Albino Rat as Affected by Feeding Various Ductless Glands (Thyroid, Thymus, Hypophysis, and Pineal)	Asst. prof. of anatomy, Yale. Deceased 1920
1917	CHESTER ARTHUR STEWART (C. M. Jackson)	Studies of the Effects of Inanition upon Growth in the Albino Rat	Prof. and director of pediatrics, Louisiana State Univ. Deceased 1946
1921	HOMER BARKER LATIMER (C. M. Jackson)	The Postnatal Growth of the Body, Systems, and Organs of the Single-Comb White Leghorn Chicken	Prof. of anatomy, Univ. of Kansas. Emeritus 1952
	HJALMER LAURITS OSTERUD (C. M. Jackson)	The Postnatal Growth and Development of the Reproductive Tract in the Female Albino Rat	Prof. of anatomy, Med. Coll. of Virginia. Emeritus 1950.
1923	HALBERT LOUIS DUNN (R. E. Scammon)	The Growth of the Cerebrum and Its Integral Parts	Chief, National Office of Vital Statistics, U.S.P.H.S.
	SHIRLEY PUTNAM MILLER (C. M. Jackson)	The Effects of Inanition upon the Stomach and Intestines of Albino Rats Underfed from Birth for Various Periods	Asst. prof. of anatomy, Univ. of Minnesota. Emeritus 1946

PH.D. DEGREES GRANTED — *Continued*

<i>Date</i>	<i>Name (Faculty advisor)</i>	<i>Title of thesis</i>	<i>Most recent position</i>
	GUSTAVE JOSEPH NOBACK (R. E. Scammon)	A Study of the Developmental Anatomy of the Respiratory System in Man	Prof. and head of anatomy, New York Univ., and Univ. of Puerto Rico. Deceased 1955
1926	WALTER PAGE COVELL (A. T. Rasmussen)	Quantitative Studies of the Human Hypophysis	Prof. of otolaryngology, Washington Univ., St. Louis
	WILLIAM THOMAS PEYTON (R. E. Scammon)	Developmental Topographical Anatomy of the Head and Neck of the Fetus, the Newborn, the Child, and the Adult as Determined by the Orthoscopic Method	Prof. of neurosurgery, Univ. of Minnesota. Emeritus 1960
	GORDON HATLER SCOTT (R. E. Scammon)	A Quantitative Study of the Growth Changes of the Parts of the Human Fetal Stomach Wall	Dean, College of Medicine, Wayne State Univ.
1927	CHARLES HAMILTON WATKINS (R. E. Scammon)	A Quantitative Study of the Growth of the Arterial System of the Human Fetus with Respect to Body Length, Body Weight, and Age	Prof. and head, section of Internal Medicine, Mayo Clinic
1929	DONALD DUNCAN (A. T. Rasmussen)	Studies of Degeneration in the Peripheral Nerves of Normal Mammals	Prof. and head of anatomy and assoc. dean, Graduate School, Univ. of Texas, Galveston
	CARROLL EDWARDS PALMER (R. E. Scammon)	Studies on the Center of Gravity in the Human Body	Director of research, Tuberc. Div., U.S.P.H.S.
	HAROLD EWART ROE (R. E. Scammon)	The Prenatal Development of the Skin and <i>Tela-Subcutanea</i> in the Human Fetus	Pediatrician, Pomona, California
1931	CLAY BRISCOE FREUDENBERGER (C. M. Jackson)	Differences between the Wistar Albino and the Long-Evans Hybrid Strains of the Norway Rat	Prof. and head of anatomy, Univ. of Utah. Deceased 1946
1932	CHARLES MORRIS BLUMENFELD (C. M. Jackson)	Effects of Various Dietary Deficiencies Upon the Morphology of the Suprarenal Gland	Pathologist, Sutter General Hosp., Sacramento, Calif.
	BYRON ELLSWORTH HALL (Hal Downey)	Certain Phases of the Monocyte Problem	Internist, San Francisco, and assoc. clin. prof. of medicine, Stanford Univ.
	SAMUEL IRVING STEIN (A. T. Rasmussen)	The Effects of Pregnancy on the Hypophysis of the Albino Rat	Neuropsychiatrist, Chicago, Illinois
1934	RUSSELL LOWELL JONES (A. T. Rasmussen)	The Structure of the Vagus and Glossopharyngeal Nerves	Director, Medical Dept., Motion Picture Relief Fund, Inc., Los Angeles, Calif.
	JOHN JOSEPH LAWLESS (A. T. Rasmussen)	Effects of Castration on Organ Weights in the Rat	Assoc. prof. of medicine and dir. Univ. Health Serv., Univ. of West Virginia
1935	OLIVER PERRY JONES (Hal Downey)	Erythroblasts with Special Reference to the Megaloblast	Prof. and head of anatomy, Univ. of Buffalo
1936	OSCAR ARNOLD BILLETER (C. M. Jackson)	The Effect of Spaying and Theelin Injections on Body Growth and Organ Weights of the Albino Rat	Plastic surgeon Salt Lake City, Utah
	ARTHUR KIRSCHBAUM (Hal Downey)	Blood Cell Formation in Mammalian Embryos	Prof. and head of anatomy, Baylor Univ. Deceased 1958

P.I.D. DEGREES GRANTED — *Continued*

<i>Date</i>	<i>Name (Faculty advisor)</i>	<i>Title of thesis</i>	<i>Most recent position</i>
	RAYMOND A. SCHWEGLER, JR. ^o (E. A. Boyden and J. C. Litzenberg)	The Development of the Duodenal End of the Common Bile Duct in the Human Embryo and Fetus with Special Reference to the Origin of the Ampulla of Vater and Sphincter of Oddi	Obstetrician and gynecolo- gist, and clin. assoc. prof., Univ. of Kansas, Lawrence-Kansas City
	HERBERT WALD (Edith Boyd)	The Normal Variability of the Weight of the Kidneys, and the Effect of Path- ological Processes upon the Distribu- tion of the Weight of the Kidneys	Surgeon Louisville, Kentucky
1937	DAVID SMITH JONES (E. A. Boyden)	The Origin of the Sympathetic Trunks in the Chick Embryo	Prof. of anatomy, Loyola University, Chicago
1939	JEFF MINCKLER (A. T. Rasmussen)	The Nerve Terminals of the Human Spinal Cord (Normal and Pathological)	Director of laboratories, General Rose Memorial Hosp., Denver, Colorado
	RUSSELL LEROY MOSELEY (A. T. Rasmussen)	Innervation of the Pancreas	Pathologist, VA Hospital, Pittsburgh, Pennsylvania
	NORMAN D. SCHOFIELD (R. F. Blount)	Transplantation of the Pancreatic An- lage in the Urodele Embryo	Pathologist, Austin State Hospital, Austin, Texas
	RAYMOND CARL TRUEX (A. T. Rasmussen)	The Structure of Sensory Ganglia with Special Reference to the Incidence of Multipolar Neurons	Prof. of anatomy, Temple Univ.
1940	YU-CHI WANG (R. E. Seammon)	A Comparison of the Surface Area and Parts of the Cerebrum in Differ- ent Races	Returned to China. No current information.
1941	GRANT LITSER RASMUSSEN (A. T. Rasmussen)	I. The Origin, Course and Destination of the Olivary Complex. II. Fiber Pro- jections of the Olivary Complex	Chief, Sect. Functional Neu- roanatomy, Inst. of Neurol. Dis. and Blindness, Nat. Insts. of Health
1942	THOMAS FRANCIS DOUGHERTY (Hal Downey)	Studies on the Cytogenesis of the Mi- croglia; Their Relation to Haematoge- nous Cells and to the Cells of the Reticuloendothelial System	Prof. and chairman of anatomy, Univ. of Utah
	ERLING STANFORD HEGRI (R. F. Blount)	The Relation of Age to the Influence of the Diencephalic Floor upon Hy- pophyseal Development	Prof. and chairman of anatomy, Medical College of Virginia
	ROBERT LYNN MERRICK (A. T. Rasmussen)	A Quantitative Study of the Supra- optic Nucleus of the Rats, Dogs and Humans	Neurosurgeon, St. Paul, and asst. clin. prof., Div. of Neu- rosurgery, Univ. of Minn.
	CHARLES ROBERT NOBACK (R. E. Seammon)	The Development of the Human Os- seous Skeleton During Embryonic, Fe- tal and Circumnatal Periods	Assoc. prof. of anatomy Columbia Univ.
	MELVIN A. SCHADEWALD (A. T. Rasmussen)	The Structure of the Blood Vessels of Human Stellate Ganglia and Its Chan- ges with Age	Asst. prof. of anatomy, Univ. of Texas, Galveston. Deceased 1954
1943	GLENN A. DRAGER (A. T. Rasmussen)	The Innervation of the Anterior Lobe of the Hypophysis Cerebri	Neurologist, Univ. of Texas Medical Branch Hospitals, Galveston
	ROBERT GORDON GRENELI (A. T. Rasmussen)	The Effects of Temporary Arrest of the Circulation on the Brain	Prof. of neurobiology and psychiatry, Univ. of Mary- land

^oPh.D. in Obstetrics and Gynecology, Thesis in Anatomy

PH.D. DEGREES GRANTED — *Continued*

<i>Date</i>	<i>Name (Faculty advisor)</i>	<i>Title of thesis</i>	<i>Most recent position</i>
	RUTH DOROTHY SUNDBERG (Hal Downey)	Lymphocyto-genesis in Human Lymph Nodes	Prof. of anatomy, Univ. of Minnesota
	CHARLES VAN BUSKIRK (A. T. Rasmussen)	A Quantitative Study of the Seventh Cranial Nerve Complex in Cat, Dog, and Man	Prof. of neurology, Univ. of Maryland
1944	ROBERT HARRISON REIFF (Hal Downey)	Splenomegaly of the Banti Type	Pathologist, Seattle, Washington
1947	ROBERT ALAN GOOD (Betty Campbell)	The Morphologic Mechanisms of Hyperergic Inflammation in the Brain: with Special Reference to the Significance of Local Plasma Cell Formation	Prof. of pediatrics, Univ. of Minnesota
	JOHN WALTER REBUCK (Hal Downey)	Cytology of Acute Inflammation in Man as Demonstrated by Two Original Technical Procedures with Particular Reference to the Role of Lymphocytes	Pathologist, Henry Ford Hospital, Detroit
1948	SISTER TERESITA JUDD (Arthur Kirschbaum)	A Comparative Study of the Effects of Certain Chemical and Physical Agents on Mouse Leukemia	Prof. and chairman of biology, St. Catherine's College, St. Paul, Minnesota
1949	MARTHELLE JANE FRANTZ (Arthur Kirschbaum)	Adrenal Cortical Adenomas of Inbred Mice	Pathologist, Mercy Hospital, Toledo, Ohio
	HOWARD ARTHUR MATZKE (A. T. Rasmussen)	The Course of the Fibers Arising from the Nucleus Gracilis and Cuneatus of the Cat	Prof. of anatomy, Univ. of Kansas, Lawrence
1951	RALPH LLOYD KITCHELL (L. J. Wells)	Effects of Hormones upon the Adrenals and Reproductive Organs of the Fetus	Prof. and head of Veterinary Anatomy, Univ. of Minnesota, St. Paul
	FRANKLIN ROBERT SMITH ^o (E. A. Boyden and H. K. Gray)	An Analysis of Variations of the Segmental Bronchi of the Right Lower Lobe of Fifty Injected Lungs	Thoracic surgeon, and clin. assoc. prof., Univ. of Washington, Seattle
1952	MORTON ALPERT (W. L. Williams)	Observations on Some Factors in the Deposition of Ceroid Pigment in the Mouse	Prof. of anatomy, Indiana Univ.
1953	HAROLD BRODY (Betty Campbell)	Age Changes in the Cerebral Cortex	Assoc. prof. of anatomy, Univ. of Buffalo
	NATHANIEL AVROM BUCHWALD (Betty Campbell)	Studies on the Electroarchitectonics of the Cerebral Cortex	Sr. fellow, Dept. of Anatomy, U.S.P.H.S., UCLA
	SAMUEL OWEN CORNWELL (W. L. Williams)	Studies on Reticuloendothelial Function with Colloidal Gold	Pediatrician, John Umstead Hospital, Butner, North Carolina
	JOHN BASKERVILLE HYDE (Betty Campbell)	The Fifth Nerve of the Shrew	Bio-Sciences Information Exchange, Smithsonian Inst.
	DENNIS JAMES KANE (W. L. Williams)	Histopathology of the Renal Lesion in the Generalized Schwartzman Phenomenon	Instructor in medicine, Univ. of Minnesota, and chief of medicine, Ancker Hospital, St. Paul
	MARIA RYZEN (Betty Campbell)	Analysis of the Cerebral Cortex in <i>Sorex pacificus pacificus</i>	

^oPh.D. in Surgery (Mayo Clinic), Thesis in Anatomy

PH.D. DEGREES GRANTED — *Continued*

<i>Date</i>	<i>Name (Faculty advisor)</i>	<i>Title of thesis</i>	<i>Most recent position</i>
	RICHARD HANAWALT SWIGART (W. L. Williams)	Normal and Denervated Skeletal Muscle, and Connective Tissue of Mice Studied by Histochemical and Vital Staining Methods	Assoc. prof. of anatomy, Univ. of Louisville
1954	MARTHA PITEL (E. A. Boyden)	Variations in the Bronchovascular Patterns of the Left Lower Lobe of Fifty Lungs	Asst. prof. of nursing and anatomy, Univ. of Rochester, New York
1955	RICHARD GUYTHIAL HIBBS (J. F. Hartmann)	Development of the Ultra-Structure of Cardiac Muscle	Asst. prof. of anatomy, Tulane University
	JEROME SUTIN (Berry Campbell)	Electrophysiological Studies of Cerebral Cortical Function: The Regulatory Role of the Supragranular Layers in the Control of Infragranular Pyramidal Cell Excitability	Asst. prof. of anatomy, Yale Univ.
	ALBINA ANN YAKAITIS (L. J. Wells)	An Experimental Study of Growth of the Adrenals in Fetal Rats	Asst. prof. of anatomy, Univ. of Miami
1956	MONA LUYTEN COETZEE (L. J. Wells)	Hypophysis-Adrenal System in the Fetal Rat: An Experimental Study of the Hypophysis	Part-time research assistant in anatomy, Univ. of Pittsburgh, Pennsylvania
	NANDKUMAR H. KESWANI ^o (W. H. Hollinshead)	The Phrenic Nucleus in the Cat and Man	Prof. of anatomy, All-India Inst. of Medical Sciences, New Delhi, India
	ROLAND DARRELL MEADER (W. L. Williams)	A Histologic Study of Choline Deficiency in the Mouse	Asst. prof. of anatomy, Louisiana State Univ.
1958	UNG KEE HWANG (L. J. Wells)	Experimental Study of the Thyroid in the Fetal Rat	Lecturer in anatomy, Univ. of Queensland, Brisbane, Australia
1959	MARY JANE BUCKMAN (R. Dorothy Sundberg)	Studies on Embryonic and Fetal Hematopoiesis with Special Reference to the Goat	Instr. in anatomy, Univ. of Minnesota
	CARL THEODORE FRIZ (Arnold Lazarow)	Metabolic Studies on the Isolated Islet Tissue of the Pancreas of <i>Opsanus tau</i>	U.S.P.H.S. post-doctorate fellow, Carlsberg Laboratory, Copenhagen
	JAE NAM KIM (L. J. Wells and Arnold Lazarow)	The Effects of Experimental Diabetes and Subdiabetes on the Offspring of Rats	Instr. in anatomy, Seoul Nat. Univ., Korea
1960	CARL BLIXSETH HEGGESTAD (L. J. Wells)	The Influence of Growth Hormone upon Fetal Development in the Rat	Asst. prof. of anatomy, Univ. of Minnesota
1961	CHESTER A. GLOMSKI (R. Dorothy Sundberg)	Macromolecular Splenomegaly in the Rat: A Histologic Study with Special Reference to Tissue Iron Distribution in the Normal and Iron-Loaded Animal	Dept. of anatomy, Univ. of Mississippi

^oPh.D. in Anatomy, Mayo Foundation, Rochester, Minnesota

Twenty-six of the above students also received a master's degree in anatomy at Minnesota; in addition, 72 master's degrees were granted in the same time period, 1915-1961.

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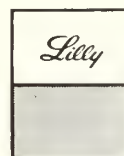
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1. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, 7:129, 1960.



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Book Reviews . . .

Pathology

W. A. D. ANDERSON, M.D., editor, fourth edition, 1961.
St. Louis: C. V. Mosby. 1,389 pages. Illustrated.
\$18.00.

The fourth edition of Anderson's *Pathology*, a multiple contributor text, has been extensively revised and is, perhaps, the most complete text on general pathology. Although the number of pages has not been increased from the third edition, the pages are larger and the type is smaller. Eliminated is the large and small type used in previous editions in an attempt to differentiate subjects of greater and lesser importance. This function is probably better served through the teacher's guidance. The 1,385 illustrations are consistently of outstanding quality, and the photomicrographs deserve special commendation.

The book is divided into 45 chapters—the first 18 on general principles of pathology and the remaining 27 on organ pathology. There are 2 new chapters. In one of these, hypersensitivity diseases and related phenomena, including collagen diseases, are discussed extensively. The other chapter includes thorough coverage of mesenchymal tumors and a fine classification of soft tissue tumors. The use of illustrations from electron microscopy heralds a new era in "every day" pathology. The bibliography is up to date and is well selected.

This text has become widely accepted in medical schools and deserves its reputation. While some may feel that the volume is too detailed and complete for an introductory course, this possible handicap should be largely obviated through the guidance of the instructors. As a ready reference text it has great value to those at all levels of experience. It is especially recommended for pathology residents and pathologists in practice, as well as to others with a special interest in pathology.

RICHARD P. LYNCH, M.D.
St. Paul

A Handbook of Social Gerontology: Societal Aspects of Aging

CLARK TIBBITTS, editor, 1960. Chicago: University of Chicago Press. 775 pages. \$10.00.

The *Handbook of Social Gerontology: Societal Aspects of Aging*, edited by Clark Tibbitts, is the second of 3 volumes dealing with the psychologic and social aspects of aging and is prepared under the auspices of the Inter-University Council in Social Gerontology.

The Handbook represents the combined efforts of 23 contributors and is divided into 3 parts: "The Basis and Theory of Social Action," "The Impact of Aging on Individual Activities and Social Roles," and "Aging and the Reorganization of Society."

The editor and contributors did a masterful job in minimizing repetition of data and in reinforcing one another. As in any handbook, however, each chapter inevitably reflects the contributor's viewpoints as to what he considers important to stress within the guideposts set by the editor. This has resulted in a variance as to how the separate topics are covered; thus the book consists of general reviews, current research and information, and areas for future studies. In addition to those who stressed only one aspect, there are several who utilized all of these approaches.

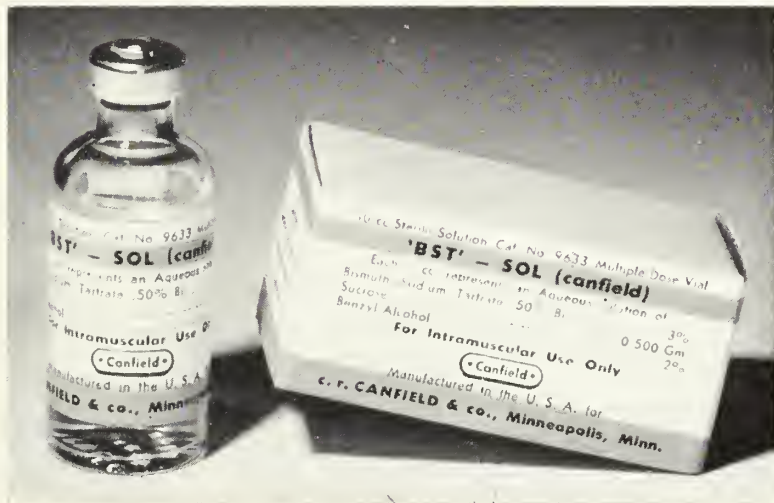
The section on "The Health Status of Aging People."

(Continued on page 18A)

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- Acute Poliomyelitis
- "Chronic Sore Throat"
- Mumps

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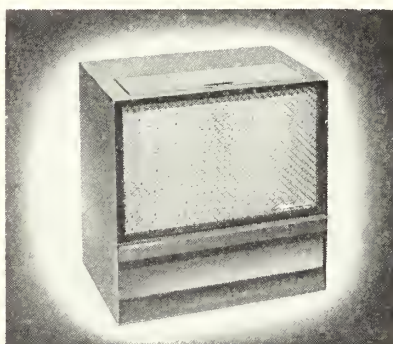
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BOOK REVIEWS

(Continued from page 16A)

by Eugene A. Confrey and Marcus S. Goldstein, is one of those combining the several approaches listed above. The chapter affirms that (1) later years bring increased amounts of disabling and chronic illness; (2) mobility and activity are limited in the later years when related to health specifics; (3) fatal accidents increase sharply with age; and (4) older adults are an integral part of the mental illness problem. The authors point out that sociologic factors may influence hospitalization of older adults. They conclude that the health of the aging is a sociobiologic phenomenon and that intensive research is needed on health and socioeconomic relationships.

Each of the other 22 chapters either directly or indirectly relates to health and the aged. Each chapter makes a major contribution to gerontology which will give the Handbook its place as a basic reference book in the study of human aging.

Clark Tibbitts, the Inter-University Council in Gerontology who sponsored the Handbook, and the contributors have accomplished a monumental task.

JEROME KAPLAN
Mansfield, Ohio

Evaluation of Drug Therapy

FRANCIS M. FORSTER, editor, 1961. Madison: University of Wisconsin Press. 167 pages. \$4.00.

This book is a report on the proceedings of the Symposium on Evaluation of Drug Therapy in Neurologic and Sensory Diseases held at the University of Wisconsin in May 1960. The first half of the book is devoted to the problems of pharmacologic and clinical drug testing and is a worthwhile contribution. It is useful reading to the clinician, giving insight into the *raison d'être* of the drugs he uses in his daily practice and permitting him to be more critical of medical articles evaluating the efficacy of drugs. Such information is essential to the informed clinician who actively undertakes to evaluate drug therapy in any condition.

The second half of the book is essentially an attempt to define certain neurologic and ocular disease states so that there will be accurate communication among neurologic clinicians. In effect it clearly demonstrates the pathetic vacuum in which we function in regard to most of these conditions, since the participants can do no more than agree on a set of terms and a classification for each symptom complex.

The book's original objective is not met, but it is a praiseworthy beginning and may stimulate more original thinking about an important clinical problem.

PERITZ SCHEINBERG, M.D.
Miami, Florida

Motor Examination of Peripheral Nerve Injuries

Y. T. OESTER, M.D., and JOHN H. MAYER, JR., M.D., 1960. Springfield, Ill.: Charles C Thomas. 89 pages. Illustrated. \$5.50.

This manual, intended to assist the relatively inexperienced physician, is based on 2,000 actual cases of peripheral nerve injuries. The text is brief, but the illustrations make the points required. This book also may be of interest to the general practitioner, enabling him to make a diagnosis with reasonable certainty and to recognize the recommended treatment of these injuries. The book is well illustrated, printed on good paper, and easily read.

JOHN S. LUNDY, M.D.
Chicago

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA,
NORTH DAKOTA, SOUTH DAKOTA, AND MONTANA

Series on PSYCHIATRY for the PRACTITIONER

Introduction

The English have developed and put into practice a number of enlightened principles in psychiatric therapy. Many of these ideas are not new, but their application and administration have been so skillful that world-wide attention has been attracted. Prominent among these advances is the "open" mental hospital. Recently I had the privilege of visiting the Fulbourn Hospital at Cambridge, England. I was impressed by its smooth operation and the high morale and enthusiasm of the staff and patients. The superintendent, Dr. Clark, kindly agreed to write this article for the Series on Psychiatry.

Burtrum C. Schiele, M.D.

Mental Hospitals Open Their Doors

D. H. CLARK, F.R.C.P.E., D.P.M.

Cambridge, England

IN THIS ARTICLE, I shall discuss the developments and changes in British psychiatry—particularly institutional psychiatry—in the sixteen years since the end of World War II. Britain has of course shared the world-wide psychiatric advances of this period—psychosurgery, the tranquilizing drugs, and, recently, the antidepressant drugs. She has also experienced the culture changes seen in all the English-speaking world—the increasing public acceptance of and interest in psychiatry, leading to an increase in the number of doctors practicing psychiatry and the gradual provision of more finance and better facilities. I shall not refer so much to these. There have, however, been certain special developments in British psychiatry, in particular the development of open doors in mental hospitals, the therapeutic community movement, and the

extension of active therapy, industrial work, and rehabilitation.

In 1948, the National Health Service was established. Although the effects of this Service on the National Exchequer and the personal relationship between the family doctor and his patient are still the subject of debate, there is no question that for the mental hospitals the Service has been all benefit. Previously, these hospitals were run by local authorities (city, town, and county councils); standards of provision, maintenance, and staffing tended to be low. Now they are part of a National Service on an equal footing with the proud general hospitals, and there is a national scale of medical and nursing salaries. When the Service began, the low levels of provision in the mental hospitals were tackled vigorously, and, for the last decade, money has been poured into them to bring their standard of living for patients and for staff up to the general level.

D. H. CLARK is medical superintendent of Fulbourn Hospital, Cambridge, England.

OPEN DOORS

Dr. G. McDonald Bell had always hated the restraints deemed necessary in psychiatry. He became medical superintendent of Dingleton Hospital, Melrose, Scotland, a 418-bed county mental hospital, just before the War and began experimenting with open doors. His work was halted by staff shortages during the War, but he started again afterward and, in 1949, the last ward door at Dingleton was opened. They have never been closed, and, in this hospital, taking all acute psychiatric illnesses from a large rural Scottish area, no patient has been locked up for twelve years.

In 1952, Dr. Duncan Macmillan of Mapperley Hospital, Nottingham, opened the last ward doors there, and, in 1954, Dr. T. P. Rees did the same at Warlingham Park Hospital, Croydon. By this time, open doors had become a major point of discussion, and the Royal Medico-Psychological Association held a debate when the pros and cons were aired. Everyone agreed that most of the ward doors in any hospital could be unlocked; the large numbers of quiet patients did not wander away, and the elderly confused were easily controlled by good nursing. Everyone agreed that there was a great lowering of tension when the doors were opened, and the patients began to regard the staff as nurses rather than jailers. The debate was whether all doors could be opened, or whether one locked ward should be maintained in each hospital. All conceded that there were always a few patients whose mental state was such that they could not be allowed full liberty, but the open door enthusiasts said that they could easily be managed by intensive nursing and active medical treatment and that it was better that 1 or 2 patients should spend rather longer in bed than that 50 or 100 should be locked up.

It was about this time that the value of tranquilizing drugs became clear, and their use spread widely. In the acute wards, they changed the handling and the prognosis of the acute psychotic episode. On the long-stay wards, they reduced tension and made contact possible with patients long withdrawn. All this made the open door development easier and faster.

Gradually, more hospitals opened their ward doors. In the Annual Report for 1956, the Ministry of Health reported that 7 out of the 106 designated (that is, mental) hospitals in Britain were open door hospitals. The number has steadily increased; there are no definite recent figures, but it would probably be accurate to say that about 20 of the psychiatric hospitals have all

their doors open. In the majority of the others, there are only 1 or 2 doors locked. The vast majority of the psychiatric patients in Great Britain are not under lock and key.

LIBERTY

Another aspect of liberty is the patients' legal status. The majority of psychiatric patients in Britain today are not legally detained.

Until 1930, a patient requiring treatment could only enter a mental hospital as a certified patient, committed on an order given by a magistrate (Justice of the Peace) on the recommendation of a doctor. In 1930, the Mental Treatment Act made it possible to be a "voluntary patient." In the years after the War, this provision was used more and more, and, by 1954, most patients entered hospital on a voluntary basis. Thinking psychiatrists were beginning to question whether it was necessary for all the long-stay patients to be legally detained, and Mapperley Hospital, Nottingham, proudly boasted in 1955 that not one of its 1,100 patients was permanently legally detained. All were voluntary patients or under temporary orders.

The Lunacy Acts of 1890 and 1891 still governed psychiatric practice, however, and they were beginning to creak badly. A Royal Commission was appointed in 1954 to inquire into the laws relating to mental illness and mental deficiency; they reported in 1957. A Bill was laid before Parliament in 1958, became an Act in 1959, and came fully into force on November 1, 1960. This Act clarified and codified lunacy law and its many ancient provisions. No more formality is now required to enter a psychiatric hospital than is required to enter a general hospital. The majority of patients enter as "informal patients" and remain on that basis with the right to leave whenever they wish. If a patient has to be taken to hospital compulsorily, this is done by a petition supported by 2 medical recommendations. This is usually a twenty-eight-day "admission for observation" in the first instance. There are provisions by which a patient can be detained for longer, also on 2 medical recommendations. All the long-stay patients have been reviewed, and most of them have stayed on quite happily as informal patients, under no legal restraint, though for a few it has been retained.

ACTIVE THERAPY

During the years immediately after the War, interest again turned to the methods of active therapy based on the work of Hermann Simon of Gutersloh, Germany, in the 1920s and the Dutch hospitals in the 1930s. Occupational therapy had

been introduced to English mental hospitals in the 1930s, but, in many places, it meant rug and basket making for recent admissions. Work for patients was even in some disrepute because of the suspicion that it meant exploitation of the paupers. As interest began to turn to the "chronic wards" of the hospital, pioneers began to re-develop the methods of active therapy.

A landmark in this work was the publication of the 1953 Third Report of the Expert Committee on Mental Health of the World Health Organization on the Community Mental Hospital. This committee was led by 3 outstanding men, Rees of Warlingham Park Hospital, England, Kraus of Groningen, Holland, and Sivadon of Neuilly Sur Marne, France, and it set out their ideas on the running of a mental hospital.

They stressed that the most important thing about a psychiatric hospital was its atmosphere. This, they said, arose from the human relationships within the hospital and were the special responsibility of the medical superintendent. They laid down certain principles in establishing this atmosphere:

1. Freedom. The patients should be assumed to be trustworthy until the contrary is shown. They condemned locked doors, security, grills, high walls, armor-plated glass—"all the other paraphernalia of the prison"—which they said made the patients want to escape.

2. Responsibility. They stressed how important it was that patients be given all the responsibility they could manage—personal responsibility for belongings, money, and so forth; responsibility for small decisions such as what to eat or wear or buy; responsibility for running hospital activities, clubs, and meetings.

3. Activity. There must be a full job of work for everyone to do, to the limits of his capacity, and tasks for all grades of patients, supervised and carefully planned.

4. Preservation of the patient's personality. They condemned the stripping technique—clothes, belongings, money, teeth, and even hair—that were traditional in the name of good order and hygiene and stressed the importance of giving the patients personal dignity, self-respect, and a sense of identity.

5. Public relations. They stressed the importance of opening the hospital to visitors, the press, interested groups of laymen, and others and bringing the neighboring community into a healthy relationship with the hospital.

These principles have been widely applied in England during the last decade. Some hospitals

advance in one direction, some in others. Some have brought industrial work into the hospital, and hundreds of "demented" psychotics are to be found doing assembly line tasks up to factory standards; at other hospitals, dozens of patients go out to work in nearby towns. "Habit training," the inculcation of a regular routine of working, feeding, living, and excreting has been applied to the very withdrawn patients, so that the problem of incontinence in schizophrenics has now been eliminated in most hospitals. Numerous clubs, activities, and projects have been organized—patients' magazines, cookery classes, choral singing groups, drama groups, Women's Rural Institutes, and the like.

Some of these things have been done before, but in the past they were confined to the small group of elite patients. The difference is that this is now applied throughout the hospital. In the best English mental hospitals, no patient is regarded as hopeless, and there is a constant drive to move all toward discharge or at least a free and independent life within the hospital.

REHABILITATION

Rehabilitation of chronic psychotics, many of them schizophrenics who have spent many years in the hospital, is being actively pursued. Two national factors, full employment and the Welfare State, have helped us greatly in this. When there are no unemployed, it is much easier for the recovering patient to find a job; in the Welfare State, there are many social workers and resettlement officers whose task is to find jobs for the handicapped. Many mental hospitals use local factories and the Industrial Rehabilitation Units of the Ministry of Labour to fit patients for work; others send patients out to work or place them in halfway houses and other hostels.

THE THERAPEUTIC COMMUNITY

This term has been much used in Britain in the last decade. It was used in the WHO report to describe the ideal mental hospital. It had been used earlier, however, by Maxwell Jones to describe his unique experimental unit for patients with personality disorders at Belmont Hospital, near London. The term is now usually used to describe a small group of patients and staff, often in a ward or a group of wards, working together to explore relationships and to establish social recovery.

Although this movement sprang from the libertarian and equalitarian atmosphere of Britain during and after the War, it takes its theoretic justification from the studies of the social psychologists and social anthropologists. Several of

these social scientists have since worked in therapeutic communities, analyzing their function and contributing toward their development.

Their studies showed that the usual mental hospital structure of nurses, doctors, and patients with the traditional medical and nursing attitudes (especially when numbers are large and finances restricted) develops a rigid authoritarian organization and a mobility-bound hierarchy with severe blockages of information that lead to a repressive custodial attitude throughout, producing directly a resentful dependence in the patients and indirectly leading to brutalities, abuses, and violence.

Maxwell Jones' 100-bed Unit was developed for the psychopaths, persons not mentally disordered but so disturbed in their personalities that they were constantly in conflict with organized society. In the Unit, all was settled and handled in group discussion where free criticism of all, especially doctors and nurses, was tolerated and encouraged. All staff were addressed by Christian names (most unusual in England), and matters were decided by the group as a whole. Psychodrama and group therapy were used with mutual exploration of difficulties. Antisocial behavior in particular was constantly analyzed by the group in which it occurred. The methods of the Unit, often with modifications, have been applied in the mental hospital wards. Self-governing wards of long-stay and convalescent patients are fairly common. Many neurosis units are run as therapeutic communities with nearly all psychotherapy being done in the group and often by the group. Many experiments are going on to see how far these principles apply to other groups.

A LOCAL EXAMPLE

National trends are impressive but lack impact. It is therefore perhaps of value to give a few facts about one hospital as an example.

Fulbourn Hospital has served the Fen Area of England for one hundred and two years. It has now a catchment population of 376,000 in a scattered rural area of 1,356 square miles. It is the only inpatient psychiatric facility in the area, and it therefore contains the usual mixture of acute and chronic functional psychoses, senile psychoses, psychoneuroses, and personality disorders to be found in any general purpose psychiatric hospital.

In 1945, there were 805 patients and 220 admissions. By 1950, the admissions had risen to 554, but the number of resident patients was now 918. By 1960, the admission rate was 1,012, but the resident population had fallen to 870.

In 1945, there were 17 wards, all locked. In 1951, 3 were unlocked; in 1955, 2 more; by 1958, all were unlocked. In 1945, there were 6 padded rooms in use and there were one hundred and twenty-eight hours of seclusion booked. In 1958, the last padded rooms were removed, and there has been no seclusion since. On December 31, 1945, there were 31 voluntary patients in the hospital and all the rest were certified. On December 31, 1960, there were 3 patients under long-term legal detention in the hospital, 14 under twenty-eight-day observation orders, and all the others were on an informal basis.

From November 1, 1960, the date the Mental Health Act came into force, until March 1, 1961, 425 patients were admitted. Of these, 87 (21 per cent) were brought to hospital by compulsion, all under twenty-eight-day orders. On March 1, there were 3 patients in Fulbourn under long-term detention, 12 under twenty-eight-day orders, and 822 patients were on an "informal" basis—that is, under no compulsion at all.

In 1945, only a few privileged patients were allowed out of the grounds, and patients were forbidden to have money. A limited number of patients worked in the hospital, but 300 patients were classed as "unemployable." In 1960, every patient had an occupation; the only ones not occupied were those who were ill in bed. The very elderly attended a "Darby and Joan" Club. The severely impaired patients worked in construction gangs or attended gymnastic classes. Better integrated patients worked in hospital departments, occupational workshops, carpenter shops, and laundry; 25 patients were engaged on paid industrial assembly work within the hospital, and 30 went out to work in Cambridge every day. All patients have money and freedom to spend it at the hospital canteen, and, apart from about a dozen, all patients who can and wish to are able to go into Cambridge when they will.

RESULTS

Some of the results of this work have already been indicated. The humanization of the barbaric and bizarre world of the old mental hospitals, the disappearance of all the brutal apparatus of coercion and the prison precautions are achievements enough to those of us who remember the old days. Changed methods of organization have brought a completely different spirit of teamwork between patients, nurses who are no longer jailers, and doctors who have abandoned at least some of their medical omnipotence. Other results are coming now. The numbers of patients in mental hospitals are falling; some large mental

hospitals have had a 20 per cent reduction in their numbers. Many patients, although odd and psychologically crippled, are now living in the community instead of rotting their lives away in institutions. It seems that we have learned a better way of treating acute schizophrenia and maintaining the chronic schizophrenic in a full and active life.

The mortality of functional psychoses has changed in the last decade. Before then there was a steady, though not high, death rate from exhaustion, pneumonia, violence, and suicide among people of young and middle age in mental hospitals suffering from recoverable psychoses. Now this has largely disappeared. Some of this has been due to the tranquilizers, making the very acute and disturbed psychotic more manageable, and to the antibiotics which control intercurrent infection, but the open door hospital has also eliminated the undercurrent of tension and covert violence which led to homicides, fractures, and the suicides of protest. Suicide is still a problem but occurs less often since we have got rid of the antisuicidal precautions, which often made the problem worse by focusing the patient's attention upon his plight.

GENERAL

This picture has been mostly confined to the mental hospital; there have, however, been changes in both the allied field of mental deficiency and community attitudes and provisions.

Rehabilitation has been most effective in the mental deficiency institutions. There are now few feeble-minded (morons) in institutions; the majority of them are at work and living in their homes or in special hostels. The only ones still in institutions are the small antisocial group, and, for them, modifications of the therapeutic community method are being found effective. For the imbecile group, industrial work has been found suitable. The idiot group, of course, is increasing with improved medical care and proving an increasing nursing burden.

The Mental Health Act applied the same legal code to the mentally defective as to the mentally ill. Henceforth, they are to be called subnormal (moron) or severely subnormal (idiot and imbecile). For them, too, informal admission has proved possible, and only markedly antisocial patients are now legally detained.

Public attitudes have changed greatly. With open doors, free visiting, and rising admission rates, many come to see the hospitals, and Open Days, Visitors Weeks, Mental Health Weeks, and other devices have brought many who have been amazed to find the mental hospital quite

unlike their dreary imaginings. There have been films, books, and television programs especially during Mental Health Year, 1960. Bodies such as the National Association for Mental Health keep up a constant educational drive, and there has been constant pressure in Parliament on the Minister of Health to increase the allocation of funds for mental health. It is these changed public attitudes—based finally on the fact that the mental hospital is different from what it used to be—that has made some of the advances possible. Because of public acceptance, there has been little outcry against open doors; because of public acceptance, patients will come to hospital and remain there willingly; because of public acceptance, it is possible for the rehabilitated patient, eccentric and schizoid though he may be, to find work and lodgings.

FUTURE

This is always difficult to predict. It seems certain that the numbers of psychiatric inpatients will decline, and the fall may be dramatic. The Minister of Health recently stated on expert advice that he expected that the number of persons in England and Wales requiring inpatient psychiatric care would fall from 150,000 in 1960 to 75,000 in 1975. The planners have at last learned that small units that preserve that personal touch which is the essence of all good psychiatry are truly more economic, and it seems likely that the vast asylums will be broken up. Much treatment of the future will be done in small (30 to 100 bed) units attached to general hospitals, serving small communities. In these, acute illnesses will be treated, while the chronically impaired will be carried in the community by the local authority services and the general practitioners.

Lest this article, in talking of achievement, should seem to suggest that all problems are solved, it would be wise to end with a mention of the difficulties we still face. Although we can treat the functional psychoses much better, we can still do little to prevent them; the incidence of schizophrenia has been unaltered for a century. The senile psychoses still require large facilities for custodial care and will probably always need this. The number of surviving, severely subnormal patients is increasing with developing medical skill and will require more and more care. The problem of the psychoneuroses and personality disorders increases, and the facilities, especially for adequate psychotherapy, fall far short of what is needed.

There are problems enough to keep us busy for our lifetimes.

Carotid-Basilar Anastomosis

A Report of Two Cases

LEONARD A. TITRUD, M.D.

Minneapolis, Minn.

THIS persisting abnormal congenital arterial communication between the internal carotid and the basilar artery has now been described in some 35 cases.¹ The largest series described have been by Krayenbühl and Yasargil² and by Saltzman.³ It is rather astounding how frequently this anomaly has been found in association with subarachnoid hemorrhage and with the presence of brain tumors.^{3,4,5}

During embryonic development, there are many vascular communications between the carotid and vertebral systems. Most of these gradually obliterate. The presently discussed anomaly, the trigeminal artery, so named because of its approximation to the trigeminal ganglion, may persist as a very large arterial channel connecting the cavernous part of the internal carotid to the basilar artery. Sunderland^{6,7} has demonstrated clearly such close anatomic relationship of cerebral arteries in unusual locations and the pressure effect on adjacent cranial nerves. It is conceivable, then, that a persistent trigeminal artery could disturb the function of the adjacent third, fourth, fifth, or sixth cranial nerves; and such malfunctions would be valuable diagnostically.

Dandy⁸ believed that congenital cerebral aneurysms arose at the sites of vestigial stumps where embryonic vessels had not resolved completely, leaving a point of arterial wall weakness. It is probable that where a congenital vascular abnormality occurs, as with a persisting trigeminal artery, there may well be an associated aneurysm, as in case 1.

CASE REPORTS

E. K., a 53-year-old white female, was found to have normal bilateral carotid cerebral angiograms, except that the basilar artery filled from a large branch of the carotid at the site of the usual origin of the posterior communicating artery, after a spontaneous subarachnoid hemorrhage in June, 1954. No aneurysm was seen. She had had good previous health. The patient recovered well from this incident.

Then, on the 12th of May, 1957, severe bifrontal

headache and nausea developed, necessitating hospitalization on the 18th of May, 1957. Physical and neurological examinations were normal. A lumbar puncture on the 20th of May, 1957, revealed cerebrospinal fluid without cells, protein of 24.4 mgms. per cent, negative Wassermann, and colloidal gold curve. A bilateral carotid cerebral angiogram under general anesthesia was done May 23rd, 1957. The previously observed anomalous carotid-basilar arterial communication was seen on left internal carotid injection (figures 1 and 2). Additionally, an aneurysm was visualized posterior and lateral to the left internal carotid artery, arising near the origin of the left posterior communicating artery and adjacent to the anomalous arterial trunk. The right carotid study proved normal but cross-communication through the anterior communicating artery did not occur. Surgery was done on the 27th of May, 1957, with general intratracheal anesthesia and the use of a spinal needle in the lumbar subarachnoid sac for cerebral decompression. Arfonad given intravenously lowered the blood pressure to 70 mm. Hg to facilitate mobilization of the aneurysm and occlude its neck with a large Olivocrona clip. Scarring about the 1 cm. in diameter aneurysm indicated previous bleeding. The aneurysm was located on the intracranial part of the left internal carotid artery and was directed posteriorly into the middle cranial fossa.

Convalescence was satisfactory. There was postoperative blood pressure elevation to 150/65, which gradually came down to 120/60 by the 4th of June, with the aid of chlorpromazine (Thorazine). She went home June 14th, 1957, and has been well without physical or neurological deficit since.

N. V. T., a 67-year-old white male, was hospitalized the 24th of April to the 28th of May, 1960, and complained of right headaches for the previous two months.

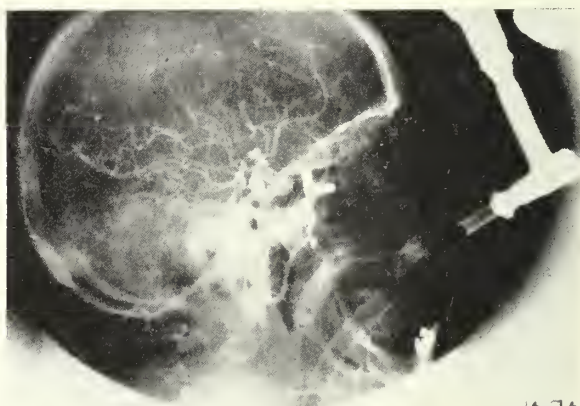


Fig. 1 (case 1)

LEONARD A. TITRUD practices neurosurgery in Minneapolis.

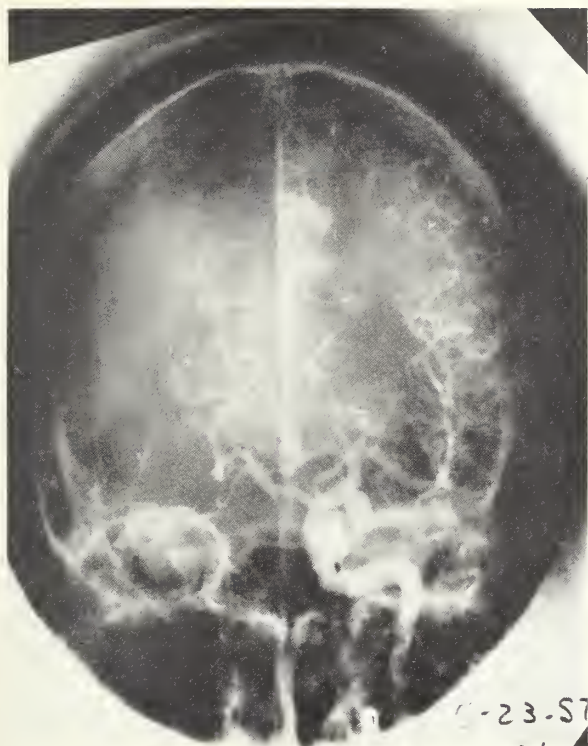


Fig. 2 (case 1)



Fig. 3 (case 2)

He developed a tendency to deviate to the left while walking. Some personality change was observed. His speech had become somewhat rambling, with incoherence and frequent change of subjects. His past health had been complicated by a duodenal ulcer, polycythemia vera, hyperthyroidism, sigmoidal diverticulosis, auricular fibrillation, and by his having had a basal-cell carcinoma of the nose excised several years before.

Physical examination revealed a large muscular, plethoric, and well-appearing person. Blood pressure was 110/58-130/70, pulse 76, respiration 20. He was hyper-reactive and talkative. General physical examination seemed normal. Neurologically, there was blurring of the medial borders of the optic disks. The left visual fields seemed reduced on confrontation testing. The left arm was weak and ataxic. The reflexes of the left arm and leg were increased, the left abdominals were decreased, and a left Babinski sign was present.

An electroencephalogram demonstrated abnormality over the right cerebral hemisphere. On the 29th of April, 1960, a bilateral carotid cerebral angiogram was done. The right middle cerebral artery was displaced upward. Both the right middle and anterior cerebral arteries were displaced toward the left. These changes outlined a large right temporo-parietal mass. Additionally, on the right, a prominent carotid-basilar arterial communication (figures 3 and 4) was demonstrated. There were no anomalous vessels seen on the left carotid angiogram. A right temporo-parietal craniotomy on the 29th of April, 1960, demonstrated marked increased intracranial pressure. At a depth of about 4 cm., a cyst was encountered in the temporo-parietal region which was emptied of about 30 cc. of a clear and yellow fluid, which clotted promptly on exposure to the air. Most of the right temporal cerebral lobe was removed. The deeper white

matter seemed gliotic and had a tan appearance characteristic of a diffuse glioma. This tissue together with parts of the cyst wall was sent to the pathology laboratory. Some fibroblastic changes in the tissue were described

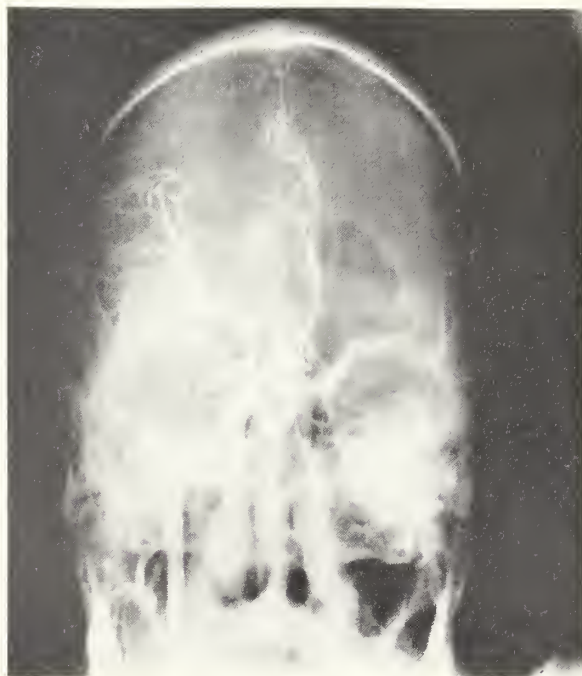


Fig. 4 (case 2)

with nothing typical of a brain tumor seen. Some angiomatous changes in the cyst wall led to a histologic diagnosis of a hemangiomatous cyst.

His convalescence was quite satisfactory, with increasing strength of the left arm and leg and improved mental status. Then, by the 3rd of May, 1960, the patient seemed nervous and demonstrated tremors of his hands. Auricular fibrillation developed, and a ventricular rate of 140 per minute occurred which improved on sedation and cardiac management. He was believed to have neck stiffness. A lumbar puncture revealed 350 mm. cerebrospinal fluid pressure to exist. This fluid had 5,350 RBC, 53 M 26 N, 354 mgms. per cent protein, and was sterile on culturing. There was good strength of the extremities bilaterally and no papilledema. Because of increased lethargy by May 8th, the craniotomy wound was explored. Nothing unusual was found except a small extradural clot which was removed. After this time, he gradually improved becoming more awake and able, and was discharged to his home May 28th, 1960.

Because of increasing difficulty, this patient was hospitalized again on the 16th of June and remained until his death July 13, 1960. After reaching home, he had improved generally for the first two weeks when drowsiness, confusion, and anorexia developed. After hospitalization, it was observed that the blood pressure was 130/70, pulse 60, and that he was incontinent. He was very drowsy but would awaken and speak and he revealed mental confusion. There was no papilledema. However, he had left hemiparesis and a left Babinski. The abdominal reflexes were absent and tendon reflexes increased. A lumbar puncture revealed no increased cerebrospinal fluid pressure. This fluid had 4 erythrocytes and 2 neutrophil and 2 mononuclear leukocytes with a protein content of 320 mgms. per cent and was sterile. On the 27th of June, 1960, a bilateral carotid cerebral angiogram showed the presence of a large right temporo-parietal mass, as indicated by the vascular displacement, quite similar to the angiogram of April 29. A right temporo-parietal craniotomy on the 28th of June, 1960,

demonstrated a moderate increase of intracranial pressure. A large firm, fibrous, vascular, and somewhat encapsulated tumor was removed from the right temporo-parietal region. This tumor appeared grossly to extend from the frontal back to the occipital lobes and very deeply into the parietal lobe. The histological study favored this to be a sarcomatous meningioma. Postoperatively, the patient remained apathetic with left hemiplegia. He did arouse to speak and regained some left leg movement. However, he followed a downhill course and died with bronchopneumonia, on July 13. Autopsy examination demonstrated tumor extension into the basal ganglia.

With this paper, two additional cases are added to the previously described carotid-basilar anastomosis. The association of this anomaly with cerebral vascular malformation or tumor is observed again.

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BECAUSE of a chromosomal abnormality in either parent, risk that young mothers of mongoloids will have another similarly affected child is high. Siblings were observed for 642 index patients (children through whom the family is ascertained). Mongolism occurred in 5 of 312 siblings born later than the index patient and in 4 of 927 born earlier; mongoloid incidence for such siblings in the general population would be 1 and 1.5, respectively. Among mothers less than 25 years of age, risk of producing a second mongoloid is about 50 times the random risk. In mothers 25 to 34 years of age, risk is increased fivefold, but no increase is apparent in mothers older than 35.

C. O. CARTER and K. A. EVANS: Risk of parents who have had one child with Down's syndrome (mongolism) having another child similarly affected. *Lancet* 2:785-788, 1961.

A Cardiac Resuscitation Program

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DURING the last five years, increasing attention concerning cardiac arrest and its treatment has appeared in the medical literature. With a more thorough knowledge of this condition and with the availability of cardiac electronic equipment, previously hopeless situations are now reversible. It is necessary, however, that all personnel be thoroughly trained in resuscitation programs and all emergency conditions adequately anticipated.

Such a program has been developed at Bethany Hospital in Kansas City, Kansas, under a title called the Code Blue Emergency. The phrase Code Blue encompasses those emergency situations which are an immediate threat to life and which can be corrected by immediate measures frequently utilizing special equipment.

The word blue was chosen since these catastrophies are usually a sudden cessation of oxygen supply to the patient. This may result from aspiration of vomitus, sudden massive blood loss, or from sudden loss of heart action, either due to cardiac standstill or to ventricular fibrillation. It may also occur from fear or other unknown neurogenic causes. Cardiac arrest is a descriptive term embracing either standstill or fibrillation, indicating an arrest in the heart's ability to pump blood and it usually results from lack of oxygen supply to the heart from one of the causes mentioned above or is due to disease of the heart itself. The patient usually appears blue or cyanotic, his pulse and blood pressure are unobtainable, consciousness and response to stimuli are lost, and unless respiration and heart action can be restored quickly, the appearance of death will rapidly proceed to true tissue death.

There is a short interval between cessation of heart action and death. If resuscitation, to the stage of providing even mechanical or assisted respiration and pulse, can be instituted within four minutes of the time of oxygen loss, there is a good chance that the patient's heart and respiratory mechanisms can be made to work again. Time is essential, for we wish not only for a living patient but for a normal patient.

After three to four minutes of anoxia the brain is damaged to a greater and greater degree and even if resuscitated, the patient may then have permanent reduction of cerebral function.

CODE BLUE PROGRAM

Our emergency term Code Blue and the personnel, equipment, and supplies that it can deliver are the means of bringing adequate treatment to the patient within these time limits. It encompasses the following groups of personnel in the hospital: the engineering department, the inhalation therapy department, the anesthesiology department, and the nursing department associated with the regular house staff. The essential supplies are provided on portable units which are called crash carts (figure 1), one being kept in the operating room theatre, and the other in the emergency room area of the hospital. The program has been divided into 3 phases: (1) prevention and treatment of cardiac arrest in the operating room-recovery theater; (2) management of cardiac arrest occurring unexpectedly on the floors of the hospital and; (3) provision for future building of an intensive coronary care area with permanent electronic features. The third part of the program is now in the process of development.

FIRST PHASE

Cardiac arrest in the operating room area is most likely to be due to either blood loss, short periods of anoxia, or unknown neurogenic mechanisms. Although cardiac arrest occurs in every patient who dies, in the operating room it is likely to occur in patients who otherwise would not die. Therefore, maximum effort should be placed first in this area in the development of any hospital resuscitation program.

The essentials of this maximum effort are: (1) the preoperative use of atropine medication; (2) pre-anesthetic attachment of patients to an Electrodyne-scope-pacemaker; (3) early recognition and institution of corrective measures as soon as arrest is suspected; (4) a method of signaling for help and additional equipment within the department; (5) constant reminders

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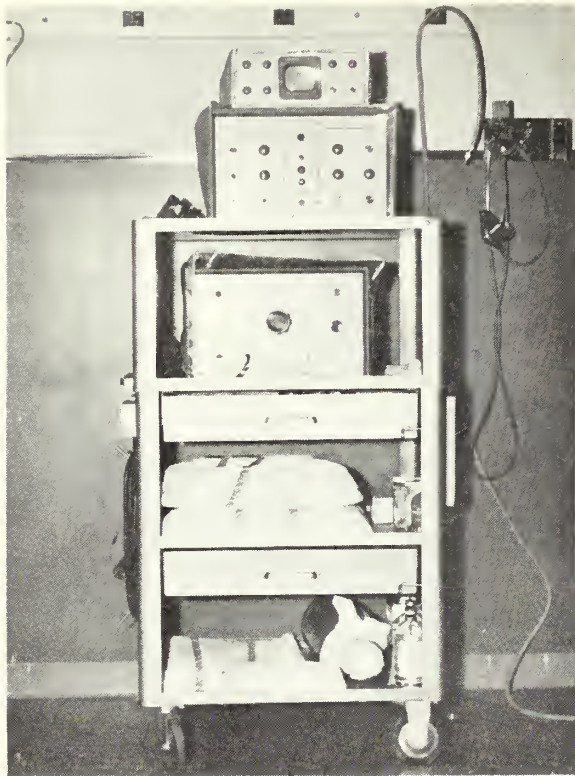


Fig. 1. Three of these mobile crash carts carrying an Electrodyne Scope-Pacemaker and an External-Internal Defibrillator are in service at Bethany Hospital.

of necessary steps in treatment when arrest has occurred.

All questionable cardiac cases are placed on an Electrodyne PM 65 scope-pacemaker prior to anesthesia induction so that we have a constant visual record of the patient's cardiac status as well as an automatic pacemaker in the event cardiac arrest should occur. A permanent record may be maintained by connecting the Electrodyne apparatus to a Sanborn cardiette. The anesthesia department is charged with the responsibility of ordering pre-anesthetic atropine prior to induction.

Nurses in the operating room theatre have been trained as to their function in the event a signal is given that a cardiac arrest has occurred. The circulating nurse remains in the operating room and assists the anesthetist by obtaining any needed equipment. She automatically sets a timer located in each operating room and also announces through a signal system, heard throughout the operating room area, that a cardiac arrest has occurred. This is then transmitted over the signal system in the hospital, using the words Code Blue—Surgery. In each operating room are removable signs for

the surgeon, listing the procedures that he is to follow. A printed "Code Blue Manual" is available for all hospital personnel and physicians and lists in detail personnel instructions. A manual is also attached to each crash cart. The cardiac arrest signs in each operating room carry the following information:

Procedure when arrest is suspected

1. Start timer at three minutes with circulating nurse calling off each minute.
2. Ventilate patient. Intubate if this has not been done.
3. Place patient in Trendelenburg position.
4. Push panic button and make announcement of Code Blue.
5. Surgeon stimulates heart.
 - a. In laparotomy try for thirty seconds via diaphragm.
 - b. In cases other than laparotomy or thoracotomy, try sternal intermittent compression for thirty seconds.
 - c. At thirty seconds open the chest at left fourth or fifth intercostal space. Split cartilages above and below and insert rib retractor. Open pericardium and manually start compressing heart at approximately 60 times per minute.
6. Follow crash cart instructions.

In the event that no cardiologist is in the hospital, the crash cart instructions list the types of drugs which can be used in cardiac arrest. These have been devised so that the surgeon need only remember that he injects 10 cc. of any particular drug. The crash cart contains vials of cardiac crash cart epinephrine (Adrenalin) with each 10 cc. containing 0.3 cc. of 1 to 1000 epinephrine. It also contains cardiac crash cart calcium chloride solution, with each 10 cc. of the solution containing 3 cc. of 10 per cent calcium chloride. If ventricular fibrillation is present, the surgeons proceed with the use of the internal defibrillator. The crash cart contains adult, child, and infant defibrillators as well as an internal pacemaker which can be utilized via the Electrodyne apparatus on the internal position. External cardiac massage in our opinion replaces the above instructions for opening the chest, and this is an optional procedure for the surgeons if he so desires to follow this course. However, the majority of our surgeons prefer to open the chest.

SPECIAL EQUIPMENT

The crash carts in Bethany Hospital are machinist's carts which have been modified by our engineering department. They are built with

grounded 5-in. caster wheels plus a small chain. Also on the carts are 3-way grounded electrical connections which accommodate both the Electrodyne pacemaker and the external-internal defibrillator. They are coated with a baked blue enamel and they contain the following equipment:

1. An Electrodyne D 72 external-internal defibrillator and a PM 65 scope pacemaker.
2. Internal defibrillator electrodes—adult, child, and infant size—in sterile package.
3. External electrodes for external defibrillation.
4. Internal electrodes for the pacemaker which can be applied directly to the ventricular surface.
5. A thoracotomy pack for opening. This contains on the outside of the pack 1 sterile scalpel. On the inside is the following equipment:
 - a. Scalpel and blades
 - b. 7-in. heavy Mayo scissors
 - c. Four curved Pean forceps
 - d. 7-in. thumb forceps with teeth
 - e. A Finechette rib spreader
 - f. Four towels with 4 towel clips and 2 half sheets.
6. A closure pack:
 - a. A Bailey rib approximator
 - b. Scalpel blades and Bard-Parker handles
 - c. A 7-in. needle holder
 - d. A 6-in. thumb forceps with teeth
 - e. Surgery scissors
 - f. Two Pean forceps
 - g. Two towel clips
 - h. Intercostal rubber tubing.
7. A cut down set including plastic cannules, sizes 15, 18 and 20.
8. A complete tracheostomy set.
9. Sterile gloves, size 8.
10. 1,000-cc. bottle of 5 per cent dextrose and water and 1 unit dextran or some other expander solution.
11. A small case containing knife blades, needles and sutures, 00 silk and No. 1 chromic catgut.
12. A case containing six 10-cc. syringes and 12 No. 20 3-in. needles in a sterile pack.
13. A case containing these vials of cardiac crash cart drugs:

Cardiac crash cart epinephrine

Cardiac crash cart calcium chloride solution

Procaine hydrochloride, 1 per cent

Quinidine gluconate

Procaine amide hydrochloride (Pronestyl)

Digitoxin

Ampoules of Vasoxyl, Levophed, Cedalomid and other pressor drugs.

14. A case containing endotracheal tubes and adapters.
15. A case containing miscellaneous non-sterile instruments, such as bandage scissors, tongue depressors, safety pins, and so forth.
16. A laryngoscope with spare batteries and spare bulbs.
17. A stethoscope.
18. Suction catheters, No. 13 straight French.
19. One Robinson tonsil suction with tubing.
20. A waterseal bottle and tubing.
21. A transistorized Medtronic pacemaker for both external and internal application.
22. Rolls of adhesive tape.
23. One sandbag.

SECOND PHASE

The second phase of the program concerns the general hospital area and applies to cardiac arrest occurring on the hospital floors, delivery room or emergency room theatre. The chief nurse in charge of the area immediately notifies the hospital switchboard that a Code Blue has occurred and gives its location. The switchboard operator repeats Code Blue twice, and the location, over the loudspeaker system of the hospital. Every thirty seconds she repeats this signal until it has been announced 3 times. Floor personnel immediately start external cardiac massage. Code Blue bedboards are on each floor and these are quickly placed under the patient's chest and head. Simultaneously, the floor personnel inserts a Hudson lifesaver tube for an airway. These are kept on all floors associated with the "Code Blue Manual" and the Code Blue bedboards. The nursing personnel have been trained to breathe for the patient at approximately 14 to 16 times per minute. This procedure is continued until the arrival of either an inhalation therapist or an anesthesiologist to operate a Bennett machine. At that time the airway is separated and the Bennett machine placed over the portion of the Hudson tube which remains in the patient's posterior throat. We have found that we have adequate oxygenation with this procedure on the floors. Upon the announcement

of the Code Blue signal, the surgical supervisor during the day brings the crash cart from the operating room area. During the evening and night hours, the night supervisor brings the Code Blue crash cart from the emergency room area. Bethany Hospital has a full inhalation therapy department with 4 full time inhalation therapists. They have been well trained to operate all Electrodyne equipment and if more than 1 inhalation therapist is present, he immediately proceeds to set up the Electrodyne-scope-pacemaker while all others maintain external cardiac massage and operate the Bennett machine. Upon the arrival of the attending surgeon or internist, the cardiac crash cart instructions for the treatment of cardiac arrest are carried out. During the hours of the night when there is a serious shortage of trained hospital personnel, the same procedures are utilized. The inhalation therapists leave the hospital at approximately ten in the evening. One Bennett machine is brought to the emergency room area and another is located strategically in the hospital. It is the duty of the night supervisor to see that the crash cart and Bennett machine are brought to the locale of the Code Blue. We have found by experience, however, that untrained personnel, or personnel not completely familiar with the Bennett apparatus can create a serious ventilation problem. The patient is therefore maintained on the Hudson lifesaver tube until the arrival of either an anesthesiologist or inhalation therapist to operate the Bennett machine and to maintain adequate oxygenation via this method.

THIRD PHASE

The third phase of the cardiac resuscitation program is just now beginning. We are in the process of completing an intensive coronary care area with funds made possible by a research

grant from the John Hartford Foundation. This will be an attempt to prove the value of electronic equipment in salvaging coronary patients who die suddenly and unexpectedly of cardiac arrest. Each coronary patient will be attached to an Electrodyne-scope-pacemaker during the first ten to twelve days of his illness. In this area will also be a third crash cart and other electronic equipment. The area is serviced through an intensive nursing program.

SUMMARY

This is a report of a cardiac resuscitation program outlining procedures, which can be followed in the operating room area and the general floors of the hospital, and of a beginning intensive coronary program made possible by the John Hartford Foundation. No deaths in the operating room-recovery theater have occurred since the institution of this program. On the general floors of the hospital the resuscitation rate is 58 per cent of unexpected cardiac arrest. However, only 8 per cent have been discharged from the hospital mentally and physically restored. The third phase of the program is just beginning and no percentage figures are available at this time.

With the rapid changes now occurring in the field of cardiac resuscitation it behooves each hospital to devise a program for the care of such cases. Errors and failures do occur, but time and experience are valuable teachers. Programs suitable for one hospital or locale may not be the answer for other institutions. However, with the vast amount of research being done, and with the modern electronic equipment available, it seems imperative that all hospitals should establish programs of cardiac resuscitation.

Acknowledgment is made to contributions of H. H. Hesser, M.D., F.A.C.S., chief of surgery, and to Francis Brochu, M.D., F.A.C.S., assistant chief of surgery.

SUSCEPTIBILITY to or duration of common viral respiratory infections is probably increased or virus viability enhanced by exposure to air pollutants measured as sulfates. A high correlation was found between the mean concentrations of suspended particulate sulfates in the air of 5 cities and the incidence of respiratory disease lasting more than seven days in women employed in those cities. Age of the women, working conditions, and social and climatic influences did not account for the variations in incidence of respiratory infections.

F. C. DOHAN: Air pollutants and incidence of respiratory disease. *Arch. Environmental Health* 3:387-395, 1961.

Analgesics in the Treatment of Postpartum Pain

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THE MANAGEMENT OF PAIN during the early postpartum period remains a daily consideration for the medical officer of any active obstetrical service. Usually the problem is not serious or prolonged and, ordinarily, good results can be obtained with any of a variety of analgesics available. Some obstetrical services use analgesics prophylactically at regular intervals during the early puerperium in all patients with the hope of preventing or minimizing any discomfort which may be associated with episiotomy, postpartum uterine contractions, or headache. When ergot derivatives are used as a routine, it is common practice to give an analgesic at the same time. On other services the use of analgesics is predicated on patient complaints.

PURPOSE

The object of this study was to review the problems of postpartum pain in consecutive patients so as to analyze the incidence of subjective complaints, the cause of these complaints, the distribution as to primipara and multipara, and then to gauge the therapeutic response to two different analgesic regimens.

METHOD

All patients received an injection of methylergonovine maleate (Methergine), 0.2 mgm., i.m., following the delivery of the placenta and ergotrate tablets, 0.2 mgm., q. 4 hrs. x 6 doses during the first postpartum day. An analgesic was given only if the patient complained of pain, alternate patients receiving either a combination of aspirin 600 mgm. plus codeine 30 mgm. or 2 tablets of Fiorinal, q. 4 hrs. as required (each Fiorinal tablet contains isobutylallyl barbituric acid 50 mgm., caffeine 40 mgm., acetylsalicylic acid 200 mgm., and acetophenetidin 130 mgm.).

Each patient was interviewed twice daily in

regard to complaints, and if she had received an analgesic, the response to medication was noted. It should be understood that all evaluations of pain and grading of severity of pain and of response to analgesic were based on the patients' subjective appreciation of pain, as well as the interpretation of the pain by the physician.

The occurrence of side effects was not sought actively but rather referred to by a general question such as "Have there been any other problems today?" This method was employed because early questioning in regard to specific possible side effects (nausea, drowsiness, vertigo, and so forth) invoked an element of suggestion yielding affirmative answers which were not genuine.

Episiotomy had been performed in approximately 90 per cent of the patients in this series, the mid-line more frequently than the medio-lateral type.

RESULTS

Two hundred and eighty-four patients were managed and interviewed as above, and of these, 127 (44.7 per cent) did not require analgesics; these patients either had no discomfort during the postpartum period or discomfort was so minimal as to obviate the need for an analgesic. This group of patients included 67 primiparas and 60 multiparas. The remaining 157 patients had significant postpartum discomfort and received either aspirin plus codeine or Fiorinal as the analgesic. Moderate to complete relief of pain was obtained as follows (tables 1 and 2):

	Uterine contractions	Headache, episiotomy pain, backache
ASA/Codeine	87.3 per cent	80.5 per cent
Fiorinal	90.2 per cent	66.6 per cent

The few patients in each group who did not derive adequate relief of pain were given Demerol 50 mgm. p.o.q. 6 hr. p.r.n.

DISCUSSION

In the treatment of ante- and intrapartum pain, maternal and fetal considerations focus atten-

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TABLE 1

Pain		—Severity of discomfort—		
		+	++	+++
Pain of uterine contractions		11	59	1
Response to ASA/Codeine	(0)	—	5	1
	(1)	—	3	—
	(2)	5	17	—
	(3)	6	34	—
Headache, backache, episiotomy pain		7	28	1
Response to ASA/Codeine	(0)	2	3	—
	(1)	—	2	—
	(2)	2	12	—
	(3)	3	11	1

Severity of discomfort is graded + for mild discomfort; ++ for moderate discomfort, and +++ for severe discomfort. Response is graded (0) for no relief; (1) for mild relief; (2) for moderate relief; and (3) for complete relief.

TABLE 2

Pain		—Severity of discomfort—		
		+	++	+++
Pain of uterine contractions		15	66	2
Response to Fiorinal	(0)	—	2	—
	(1)	—	5	1
	(2)	3	19	—
	(3)	12	40	1
Headache, backache, episiotomy pain		4	24	2
Response to Fiorinal	(0)	—	2	1
	(1)	—	7	—
	(2)	2	5	1
	(3)	2	10	—

Severity of discomfort is graded + for mild discomfort; ++ for moderate discomfort, and +++ for severe discomfort. Response is graded (0) for no relief; (1) for mild relief; (2) for moderate relief; and (3) for complete relief.

tion upon the choice of an adequate and safe analgesic. As Lull and Hingson¹ point out, postpartum pain does not always receive such consideration. Combinations of codeine with various other analgesics have been found to be effective, but where the dosage of codeine is adequate for pain relief, the compound comes under federal narcotics regulations. Fiorinal has been found to be the most effective analgesic agent tested in the treatment of tension headache.² Caldwell obtained satisfactory control of dysmenorrhea³ and of postpartum pain and discomfort⁴ with Fiorinal. This is the first comparative study using this preparation in the treatment of postpartum pain.

Two apparently valid conclusions can be derived from this study: First, approximately 45 per cent of postpartum patients required no analgesic in spite of episiotomy and the routine use of ergot derivatives during the first postpartum day. Accordingly, it would appear to be impractical and wasteful to use any analgesic prior to the complaint of pain by the patient. Second, both analgesic regimens yielded gratifying relief of pain in the large majority of patients.

It would seem reasonable to assert that the analgesic effect of ASA/Codeine is comparable to Fiorinal for relief of the discomfort associated with postpartum uterine contractions and that ASA/Codeine is slightly more effective than Fiorinal in relieving the other common discomforts of the postpartum period. It should be mentioned that the use of Fiorinal is not attended by the regulations applying to the written records required in the use of a narcotic such as codeine. Accordingly, the simplicity inherent in the administration of Fiorinal and its comparable degree of effectiveness indicate the usefulness of this non-narcotic preparation for the relief of pain in the postpartum patient.

SUMMARY

Two hundred and eighty-four patients were reviewed with respect to postpartum pain and the need for analgesics. Episiotomy was performed in approximately 90 per cent of the patients and all patients received ergot derivatives during the first twenty-four-hour period post partum.

One hundred and twenty-seven patients required no analgesic; the remainder, 157, were given one of two types of analgesics on an alternate basis and the response to these medications is reviewed and compared.

The conclusion is reached that Fiorinal is an effective preparation for the treatment of postpartum pain. Since it is a non-narcotic preparation, it has the added virtue of simplicity of administration as a practical consideration in the management of the postpartum patient.

The opinions expressed are those of the authors and do not necessarily reflect the views of the Department of the Navy.

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Neonatal Deaths in Hennepin County

A Five-Year Report

THE HENNEPIN COUNTY
PERINATAL MORTALITY STUDY COMMITTEE
Minneapolis

DEATH RATES involving infants not yet 28 days of age have not declined as rapidly as maternal death rates.^{1,2} Hence, on January 1, 1952, eleven years after inception of the Minnesota Maternal Mortality Study, the Hennepin County Neonatal Mortality Study Committee began analyzing all deaths of infants under the age of 28 days occurring in Hennepin County. In 1955 the inclusion of fetal deaths widened the period of study to cover all deaths occurring between 20 weeks' gestation and age 28 days. Since that time the group has appropriately been known as the Hennepin County Perinatal Mortality Study Committee. This report considers only neonatal deaths. The study of fetal deaths will be reported subsequently.

From its onset this committee had widespread sponsorship.³ Membership consisted of obstetricians, pediatricians, general physicians, pathologists, hospital administrators, and public health physicians. After pertinent obstetric, pediatric, and pathology data were assembled and anonymity was insured, this group considered each of the 1,710 neonatal deaths upon which this five-year report was based.

Premature infants (2,500 gm. and under) contributed nearly three-quarters (72.5 per cent) of the 1,710 neonatal deaths. Those weighing less than 1,000 gm. (2 lb. 3 oz.) comprised the largest group of neonatal deaths; 30 per cent of the five-year total were in this weight category. For each case, available information derived from special data sheets and committee discussion was transferred to McBee punch cards for easier tabulation. To facilitate comparison, many of the tables presented here are similar to those in previous reports³⁻⁶ based on parts of these five-year accumulated data.

The following statement has been repeatedly emphasized by the American Medical Association's Committee on Maternal and Child Care:⁷

The objective of perinatal mortality and morbidity studies is to improve the production of normal human beings. The elimination of deaths and damage during the process of reproduction is the ideal for which we should strive. In working toward the objective with this ideal in mind, all individuals and committees should rigidly and courteously adhere to scientific and ethical principles.⁵

The Hennepin County Perinatal Mortality Study Committee has pursued this objective by impartially and objectively analyzing neonatal deaths and attempting to make practicing physicians, hospital, and health department personnel aware of the avoidable factors associated with neonatal deaths.

The number of cases reviewed by the committee each year is shown in Table 1. The neonatal death rates are of interest, but certainly no conclusions concerning adequacy of medical care can be drawn from these varying figures. Hennepin County's neonatal death rate in each of these years was lower than the rate for the whole state.

For the first three years of the study (1952-1954) 71.8 per cent, 71.2 per cent, and 71.7 per cent, respectively, of the neonatal deaths weighed 2,500 gm. or less, whereas the percentages in this undersized group in 1955 and 1956 were 72.8 and 74.9, respectively. Probable reasons for these later increased percentages cannot be assigned without other information, but there are interesting speculations.

TYPES OF DELIVERY

The increased percentage of breech deliveries among the small infants who died before the 28th day is striking (figure 1). On these data alone no inference can be made that the type of delivery necessarily influenced mortality. Breech presentations are known to be more prevalent among premature births, and the relatively larger head and smaller body of premature infants in-

³Hennepin County Medical Society, Minneapolis Pediatric Society, Minneapolis Obstetric Society, Minneapolis Chapter of the Academy of General Practice, Minneapolis Health Department, Minneapolis Hospital Council, Pediatric and Pathology Departments of the University of Minnesota Medical School, and the Minnesota State Department of Health.

TABLE 1
ANNUAL NEONATAL DEATH RATES AND NEONATAL DEATHS
BY BIRTH WEIGHTS IN HENNEPIN COUNTY 1952-1956

Year	Neonatal deaths		Total	Live births	Neonatal death rate ^a
	2,500 gm. or less	Over 2,500 gm.			
1952	239	94	333	19,941	16.7
1953	270	109	379	20,460	18.5
1954	215	85	300	21,309	14.1
1955	259	97	356	21,968	16.2
1956	256	86	342	22,521	15.2
Totals	1,239	471	1,710	106,199	—

^aDeaths of infants 28 days or younger per 1,000 live births

crease the mechanical hazards of breech delivery. A high cesarean section rate is expected in perinatal mortality studies where complications of pregnancy and labor are naturally prominent.

The 1,239 neonatal deaths designated premature by birth weights have been further subdivided (table 2). During the first study year there was no weight breakdown beyond "2,500 gm. and under" and "over 2,500 gm." However, the totals for each type delivery of the 1952 premature neonatal deaths are included (table 2).

This premature group obviously holds the greatest potential for reduction of neonatal mortality. Premature labor cannot be conducted as full-term labor, particularly not the administration of analgesics and anesthetics to the mother. The immediate postnatal care of the premature infant is much more technical and important to survival than in the full-term infant. The recent development of successful occlusive trachelorraphy now provides another means of salvaging some babies previously classified "unavoidable disaster." Correction of incompetent cervix for some has allowed intrauterine development be-

yond the barely viable, "under 1,000-gm.," birth weight group which contributes so heavily to neonatal mortality rates.

There is something to be learned from thorough study of all premature births. Awaiting discovery are factors which will aid in prolongation of gestation, ease of delivery, and reduction of neonatal morbidity or contribute to improved care of the premature infant.

DURATION OF LIFE

Nearly 14 per cent of Hennepin County's 1952-1956 neonatal deaths occurred less than one hour after delivery (table 3). The greatest mortality for all infants, premature and full term, occurred between the ages of 1 and 24 hours. The high attrition during the first twenty-four hours (61 per cent) is graphically shown (figure 2).

Of the premature infants who did not live beyond 28 days, 82 per cent died before completing 2 days of life; only 5 per cent lived beyond a week.

Among the full-term group of neonatal deaths, more than one-third (37.6 per cent) lived past

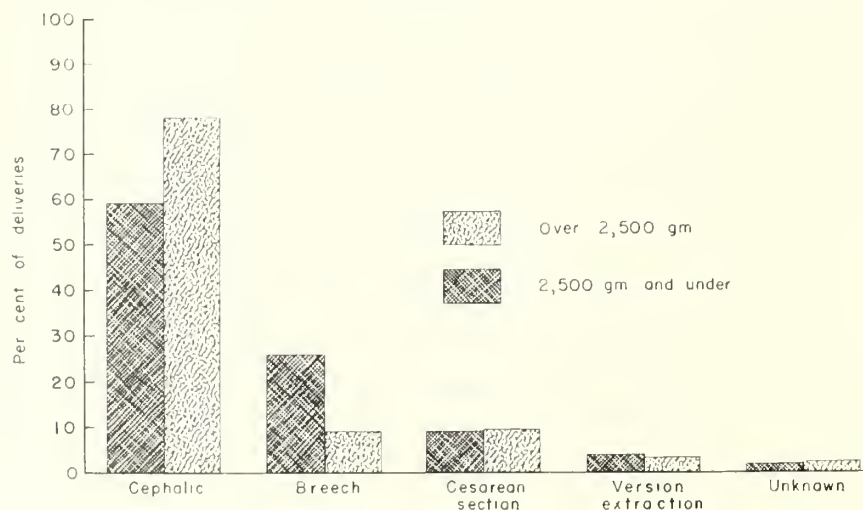


Fig. 1. Types of delivery (in per cent) for premature and full-term neonatal deaths, Hennepin County, 1952 to 1956

TABLE 2
TYPES OF DELIVERY BY WEIGHT GROUPS OF THOSE NEONATAL DEATHS
CLASSIFIED PREMATURE BY BIRTH WEIGHT
HENNEPIN COUNTY—1953-1956

Type of delivery	Under 1,000 gm.	1,000-1,499 gm.	1,500-1,999 gm.	2,000-2,500 gm.	1952 Study 1,001-2,500	Total premature
Cephalic	301	132	103	114	89	739
Breech	177	71	26	28	31	333
Cesarean	19	17	24	33	20	113
Other	9	10	7	8	1	35
Unknown	10	2	0	1	6	19
Totals	516	232	160	184	147	1,239

48 hours, and nearly 16 per cent beyond 1 week of age.

Of all neonatal deaths, 92 per cent took place during the first postpartum week.

CAUSES OF DEATH

Abnormal pulmonary ventilation continues as a predominant cause of death during the neonatal period, especially for premature infants. This classification has been used in previous reports and was suggested by Edith Potter.⁸ Included are diagnoses of immaturity, unqualified; atelectasis; and hyaline membrane disease. "Immaturity, unqualified" is the designation given to all premature infants with no recognizable extrapulmonary pathology. It is therefore not surprising that in surveying neonatal deaths among infants with birth weights of 2,500 gm. or less, 80 per cent fell into this cause category. Congenital anomalies accounted for the largest group (33.5 per cent) of neonatal deaths among those with birth weights *over* 2,500 gm. Most blood dyscrasia deaths were due to erythroblastosis fetalis, several of which might have been avoided.

TABLE 3
DURATION OF LIFE
1,710 PREMATURE AND FULL-TERM INFANTS
NOT SURVIVING NEONATAL PERIOD
HENNEPIN COUNTY—1952-1956

Duration of life	2,500 gm. and under		Over 2,500 gm.	
	Number	Per cent	Number	Per cent
Less than 1 hour	175	14.1	62	13.1
1-24 hours	652	52.6	151	32.1
24-48 hours	193	15.6	81	17.2
2-7 days	156	12.6	103	21.9
8-28 days	63	5.1	74	15.7
Totals	1,239	100.0	471	100.0

Birth trauma listed in a statistical table is exceedingly difficult to assess, and it is quite possible that the incidence of birth trauma in this study was underestimated. Physicians, hospitals, and mothers have certain capabilities of reducing these figures. Some deaths categorized "abnormal pulmonary ventilation" and "anoxia" probably were secondary to trauma. Occasionally, injuries indicating extreme approaches to

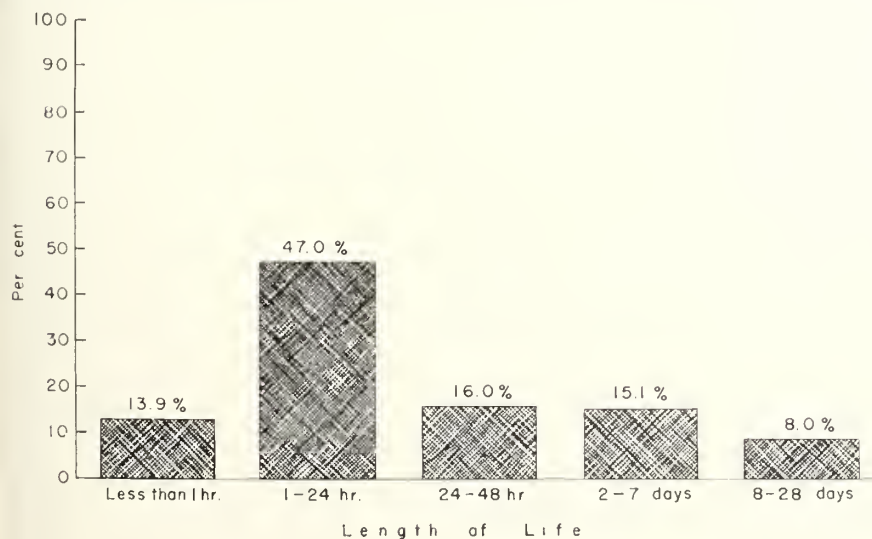


Fig. 2. Per cent of premature and full-term neonatal deaths in various survival periods, Hennepin County, 1952 to 1956

TABLE 4
CAUSES OF DEATH PREMATURE AND FULL-TERM INFANTS
HENNEPIN COUNTY—1952-1956

Cause of death	2,500 gm. and under		Over 2,500 gm.		Total	%
	Number	Per cent	Number	Per cent		
Abnormal pulmonary ventilation	991	80.0	133	28.3	1,124	65.7
Congenital anomalies	97	7.8	158	33.5	255	14.9
Infection	39	3.1	43	9.1	82	4.8
Birth trauma	43	3.5	33	7.0	76	4.4
Blood dyscrasia	20	1.6	58	12.3	78	4.6
Anoxia	25	2.0	21	4.5	46	2.7
Other	24	2.0	25	5.3	49	2.9
Totals	1,239	100.0	471	100.0	1,710	100.0

resuscitation of the newborn were evident at autopsy (table 4).

POSTMORTEM EXAMINATIONS

The constant and consistent rise in the autopsy rate of neonatal deaths is encouraging. Particularly commendable is the changing attitude toward postmortem examinations of premature infants (figure 3).

Figures already presented indicate the great loss due to early termination of pregnancy. Many premature labors had no detectable associated maternal complication, yet swelled the number of neonatal deaths classified under obstetric causes. Physiologic disturbances leading to neonatal death are most likely to occur during what might be called the obstetric period. Those infants (table 5)⁹ also for the most part were "unavoidable disasters," yet obstetric responsibility was necessarily assigned.

In recent years perinatal mortality study committees have somewhat altered methods used to fulfill their roles in professional education. The

American Medical Association's Committee on Maternal and Child Care has for some time advocated discontinuance of the practice of judging each case in terms of preventability. It has been their opinion that enumeration of "avoidable factors" associated with perinatal mortality and morbidity would be of more practical value.

To many, the chore of assigning "preventable," "non-preventable," and so forth, to each perinatal death was discouraging because it often seemed that available data would not permit such judgment by mere human beings. However, reviews of 1,710 Hennepin County neonatal deaths presented many circumstances which did not need super-human judgment to cite them as avoidable, undesirable practices.

"Avoidable factors" were found in prenatal, natal, and postnatal periods and occurred in "non-preventable" and "unclassifiable" cases as well as those labeled "preventable." Perinatal study groups have felt that deviations from accepted obstetric and pediatric standards have been important to record even though in a par-

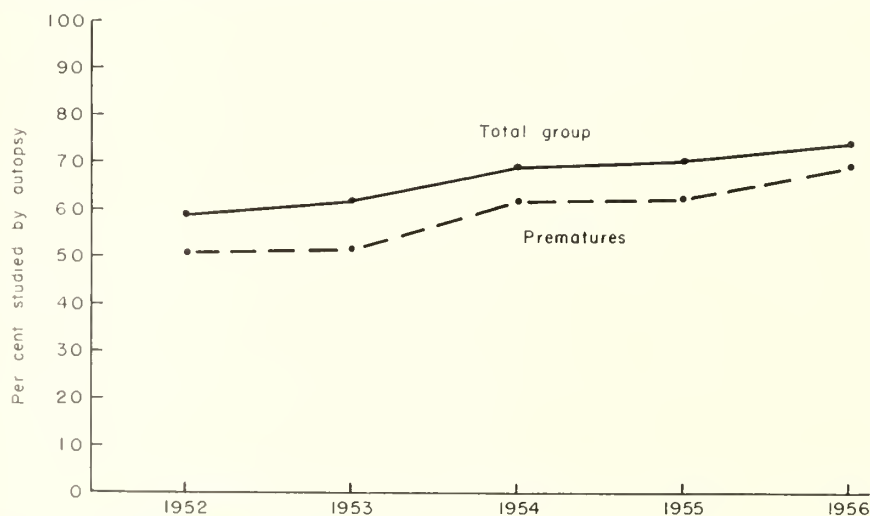


Fig. 3. Per cent of neonatal deaths studied by autopsy, Hennepin County, 1952 to 1956

TABLE 5
OBSTETRIC COMPLICATIONS
ASSOCIATED WITH PREMATURE INFANTS NOT SURVIVING 28 DAYS
HENNEPIN COUNTY PERINATAL MORTALITY STUDY—1952-1956

Complication	Weight of infant in gm.					Premature total	Full term	Total
	1,000 and under	1,001- 1,499	1,500- 1,999	2,000- 2,500	2,500 and under (1952)			
Antenatal bleeding	99	35	19	16	14	183	15	198
Abruptio placenta	44	31	23	14	23	135	14	149
Placenta previa	14	18	13	9	12	66	5	71
Toxemia of pregnancy	12	10	10	7	13	52	26	78
Infection	21	6	9	4	10	50	19	69
Polyhydramnios	8	1	6	8	6	29	14	43
Pelvic inadequacy	0	1	2	9	0	12	9	21
Prolapsed cord	7	1	5	3	1	17	9	26
Abnormality of placenta or cord	8	9	3	1	0	21	3	24
Diabetes mellitus	3	0	3	0	1	7	13	20
Other	19	4	8	5	6	42	6	48
Totals	235	116	101	76	86	614	133	747

ticular case the deviant action (or lack of action) obviously made no direct contribution to death.

Such factors are in evidence regardless of the outcome. The appearance of an "avoidable factor" in the medical history of a *surviving* infant should not dilute the seriousness of that factor.

One hundred and thirteen (6.6 per cent) of the total neonatal deaths which occurred during this five-year period were deemed preventable. Each case history in this group was perused to identify and tally the avoidable factors. Obstetric and pediatric avoidable factors (as modified from Michigan's Perinatal Mortality Study) and their occurrence among these 113 Hennepin County neonatal deaths are listed (tables 6 and 7). Avoidable factors appeared slightly more than twice in the average preventable death, and several cases demonstrated substandard practices in both the obstetric and pediatric periods.

Frequently, of course, injudicious obstetrics was assigned to a case in which other factors contributed to early death of the infant. Incorrect evaluation of size of infant prior to elective cesarean section was one of the more obvious factors. This error of judgment was the major factor in 19 neonatal deaths classified "preventable." Incorrect management of respiratory distress during the immediate postpartum period was also a major problem among preventable neonatal deaths. In 32 cases, equally divided between the obstetric and pediatric lists, it was the consensus of the committee that consultations would have changed the treatment to the advantage of the infants.

The majority of pediatric avoidable factors pertain to 2 large groups (table 7): 15 babies with sepsis and 15 babies with erythroblastosis fetalis.

Preventable factors in the latter group involved delay in recognition of the illness, poor judgment concerning indications for exchange transfusion, or hesitation to carry out treatment because of the precarious condition of the baby.

TABLE 6
FREQUENCY OF OBSTETRIC AVOIDABLE FACTORS
ASSOCIATED WITH NEONATAL DEATHS CLASSIFIED
"PREVENTABLE" IN HENNEPIN COUNTY—1952-1956

Injudicious obstetrics	56
Incorrect evaluation of size of infant	19
Improper management of resp. distress	18
Delayed or no consultation for obstetric complications	16
Inadequate prenatal work-up on Rh negative mother	8
Operative procedure without qualified consultant	6
No or insufficient antibiotic when indicated	5
Inadequate prenatal record or admission P.E.	4
Injudicious use of anesthesia in delivery	4
Failure to determine pelvic measurements	3
Injudicious use of sedation in labor	3
Improper management of hemorrhage	3
No bacteriology when indicated	3
Criminal abortion	2
Improper use of oxytocics ante- or intrapartum	2
Delayed or no consultation for medical complications	1
Improper management of toxemia of pregnancy	1
Possible homicide in unattended home delivery	1
	155

TABLE 7
FREQUENCY OF PEDIATRIC AVOIDABLE FACTORS
ASSOCIATED WITH NEONATAL DEATHS CLASSIFIED
"PREVENTABLE" IN HENNEPIN COUNTY—1952-1956

No or insufficient antibiotic therapy	20
Delayed or no pediatric consultation	16
Inadequate work-up and treatment of potential erythroblastotic	12
Failure to do indicated antemortem bacteriology	11
Delay in doing diagnostic tests in infants of Rh neg. mothers	7
Delayed or failure to do indicated x-ray examination	7
Lack of suspicion and delayed treatment for erythroblastosis	5
Improper resuscitation of infant in newborn nursery	2
Failure to do indicated laryngoscopy	2
Delayed diagnosis of pyloric stenosis	1
Delayed diagnosis of intussusception	1
Improper exchange transfusion	1
	85

Yet, apparent to this committee was the development, during the five years under study, of an appreciation in the area of blood group incompatibilities. In 1956, general awareness of potential erythroblastosis fetalis and proper treatment of cases prevailed. Few mothers gave birth to babies in our 1956 neonatal mortality group without having had an Rh factor determination (table 8).

However, there were several tragic cases of babies with sepsis in 1956.

In sepsis of the newborn, especially in premature infants, signs are so subtle and evanescent that the physician must be conditioned to include this diagnostic possibility. Etiologic diagnosis is important, and proper bacteriologic tests must be carried out early on blood, spinal fluid, stools, and urine. Prompt and appropriate treatment can then be given, hopefully in time.

SUMMARY

The Hennepin County Perinatal Mortality Study Committee reviewed all (1,710) neonatal deaths which occurred during the five-year period, 1952-1956. These cases were analyzed from several standpoints. Annual neonatal mortality rates have been presented as well as obstetric complications, methods of delivery, and causes of death associated with both premature and full-term infants. This report represents only a portion of

TABLE 8
Rh DETERMINATIONS
ON MOTHERS OF NEONATAL DEATHS
IN HENNEPIN COUNTY—1952-1956

Year	Per cent of Rh determinations done
1952	70.0
1953	68.3
1954	71.6
1955	80.8
1956	92.1

the material accumulated for this committee by Hennepin County hospitals and physicians.

The bulk (87 per cent) of neonatal deaths were classified "unavoidable disaster;" three-fourths of the deaths given such a designation weighed less than 2,500 gm. Reduction of the numbers of infants born prematurely or with major anomalies will not be easily achieved. Illumination of factors which might allow prolongation of pregnancy obviously could reduce neonatal mortality and morbidity rates immensely. Improvement in the quality of maternal and newborn records and in autopsy rates during this five-year study period reflects increased interest in this area of preventive medicine. Although certain medical practices relating to prenatal, natal, and postnatal care have tended to change in favor of the neonate, review of the 113 "preventable" neonatal deaths revealed an imposing array of avoidable factors.

To achieve our assigned goal, "the elimination of deaths and damage during the process of reproduction," a continuous program of perinatal mortality and morbidity evaluation is required.

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Incidence of Hypercalcemia in Patients with Proved Carcinoma of the Lung

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ELEVATION of the serum calcium to abnormally high levels in the presence of malignant disease has been documented with increasing frequency during the past twenty-five years.¹⁻⁵ Since the initial cases studied had osseous metastasis from neoplasms originating in various organs, the presence of hypercalcemia was attributed to the mobilization of calcium from the bones invaded by the malignant process. Because this relationship was observed so frequently, the presence of hypercalcemia alone was deemed sufficient evidence to surmise the presence of skeletal involvement.

Although this is true in the great majority of instances, a consistent elevation of serum calcium may occur without demonstrable metastatic involvement of osseous structures. Occasionally, when a diligent search is made, other causes of hypercalcemia are discovered, such as the previous ingestion of excessive amounts of vitamin D, milk, or alkali; the presence of endocrine disorders; the demonstration of other disturbances of the skeletal system; and, rarely, the concurrent presence of sarcoidosis. There is an increasing awareness, as evidenced by reports appearing during the past five years, that hypercalcemia, with its protean manifestations, may occur in the presence of malignant disease; meticulous investigations during life and subsequent examinations post mortem have failed to disclose any anatomic or physiologic explanation for this biochemical change.⁶⁻⁹ Furthermore, many of the manifestations of the hypercalcemic state which reflect derangement of organs distant to the primary malignancy dominated the clinical picture and erroneously suggested that metastatic disease was present in these distant structures.

HYPERCALCEMIA

The varied clinical signs and symptoms commonly found in the hypercalcemic state are in-

dicated in table 1. Most impressive are the manifestations resulting from disturbances of the central nervous system—change in intellect, confusion, somnolence, and episodes of coma. Diffuse alterations of the electroencephalogram may be present.¹⁰ Primary symptoms caused by disturbances in the gastrointestinal tract include loss of appetite, nausea, vomiting, and constipation. In some instances, symptoms are thirst, polydipsia, polyuria, evidence of fixation of the specific gravity, albuminuria, and renal failure. In other patients, the predominant features center about the cardiovascular system and consist of tachycardia, arrhythmia, electrocardiographic abnormalities, and increasing predilection to the toxic manifestations of digitalis administration. Finally, there are the occasional indications of altered function of the neuromuscular junction—extreme muscular weakness, hypotonia, and areflexia. In any one individual, varying degrees of involvement of one or more of the organ systems may be recognized. Since many of these manifestations mimic the deranged function of organs invaded by a malignant process, it is clear that the knowledge of the presence, as well as the effects, of the hypercalcemic state is mandatory when patients are considered for definitive therapy of their neoplastic disease.

Hypercalcemia has been associated with many types of malignant tumors. It occurs most frequently with breast carcinoma,¹¹ secondly, with primary carcinoma of the lung, currently the most common malignant tumor affecting the adult male. With this condition, hypercalcemia has appeared spontaneously, and, although skeletal metastases have been demonstrated in selected groups of these patients, a significant number have been found without this complication. It is in this latter group that a therapeutic attack of the primary malignancy may be withheld on the erroneous assumption that the presence of hypercalcemia and its perplexing manifestations represent distant metastases. With the knowledge that hypercalcemia alone can be responsible for these signs and symptoms, it becomes important

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TABLE 1
CLINICAL SIGNS AND SYMPTOMS OF HYPERCALCEMIA

<i>Location</i>	<i>Symptoms</i>
Central nervous system	confusion, disorientation, apathy, somnolence, coma, abnormal electro-encephalogram
Gastrointestinal tract	anorexia, nausea, vomiting, constipation
Renal system	thirst, polydipsia, polyuria, isosthenuria, albuminuria, renal failure
Cardiovascular system	tachycardia, arrhythmia, abnormal electrocardiogram, digitalis hypersensitivity
Muscles	weakness, hypotonia, areflexia

to ascertain the frequency with which hypercalcemia and lung carcinoma coexist and to correlate these findings with the presence or absence of skeletal involvement.

STUDY

To do this, appropriate studies were performed on consecutive patients with proved carcinoma of the lung. Chemical determinations of the serum calcium, phosphorus, and alkaline phosphatase were made not only during the early asymptomatic period of illness but during the late stages of the disease, especially when clinical symptoms suggestive of hypercalcemia were present. Table 2 briefly summarizes the results of this study; 119 patients were studied in this manner, the chemical findings being correlated with the clinical signs and symptoms of hypercalcemia as well as with the radiographic and postmortem findings of skeletal metastasis. It was quickly apparent that the vast majority of patients with this illness consistently maintained a normal serum calcium level, despite the finding that about 9 per cent of this group had radiologically demonstrable skeletal metastases.

TABLE 2
119 PATIENTS WITH PROVED PRIMARY
LUNG CARCINOMA

<i>No. patients</i>	<i>Per cent of total group</i>	<i>Serum calcium (mg. %)</i>	<i>Symptoms of hypercalcemia</i>	<i>Skeletal metastasis</i>
104	87	9.0-11.0	absent	9
13	11	11.5-13.0	absent	6
2	2	15.0-17.0	present	0

Of the 15 patients who had consistent elevation of the serum calcium, 13 had only a modest elevation—from 11.5 to 13 mg. per cent—and were entirely asymptomatic. It is of interest that this group was evenly divided as to the presence or absence of skeletal metastasis. Of significance, however, was the finding of only 2 patients, representing less than 2 per cent of those studied, who had marked elevation of the serum calcium—from 15 to 17 mg. per cent—and accordingly exhibited the classical clinical manifestations of hypercalcemia. Moreover, neither of these patients had skeletal metastasis.

In the group with hypercalcemia, the serum phosphorus was in the low or normal range and the serum alkaline phosphatase was normal. In those patients with skeletal metastasis, the serum alkaline phosphatase was elevated in only 3 instances. No consistent difference could be detected with respect to histologic cell type of tumor and extent and character of skeletal metastasis between patients with hypercalcemia and those with normal serum calcium.

The mechanism responsible for this chemical alteration is as yet unknown. Reports have appeared wherein resection of the malignancy was followed by a prompt restoration of the serum calcium to normal with dramatic disappearance of the symptoms associated with the hypercalcemic state.¹²⁻¹⁴ With the occurrence of metastases not involving the skeleton, a return of the hypercalcemia was noted. In addition, there are examples in which a well-documented hypercalcemic state was observed to disappear spontaneously shortly before death, and this was correlated with the postmortem finding of widespread necrosis of the malignant tumor.¹⁵ This remarkable relationship is strongly suggestive of a humoral agent elaborated by the tumor having the capability of selectively causing the resorption of bone. Thus far, studies of tumor tissue have failed to demonstrate the presence of such a substance.

TREATMENT

Various means have been employed in the treatment of the hypercalcemic state in patients with malignancy. The need for adequate hydration to insure maximum urinary excretion of calcium, as well as restriction of the dietary intake of calcium, is self-evident. These measures are usually not sufficiently effective alone but require supplementary procedures to restore a somnolent or comatose patient to a state of consciousness. As indicated previously, resection of the malignancy when feasible will offer prompt symptomatic improvement. In patients with

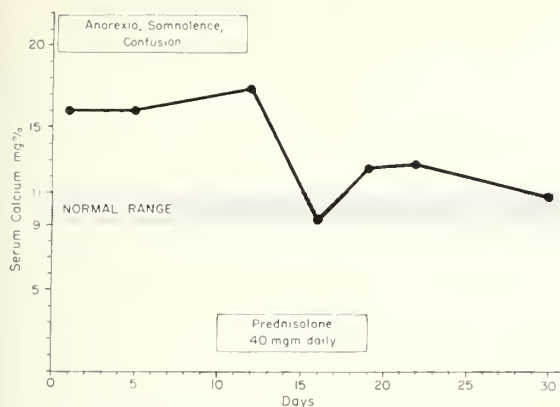


Fig. 1. Effect of steroid therapy on primary carcinoma of lung and hypercalcemia.

nonresectable malignancy, use of chemotherapeutic agents has also resulted in temporary improvement.^{16,17} Steroid therapy has been occasionally successful in lowering the serum calcium, with a response similar to that observed in sarcoidosis.¹⁸⁻²¹ This effect was achieved in 1 of the 2 patients with marked hypercalcemia in the present study and is illustrated in figure 1. The prompt fall of the elevated calcium to normal levels and the disappearance of the manifestations of hypercalcemia were again noted. This response was not observed in the second patient in our study.

Two other agents which have been employed in this condition include sodium phytate and disodium ethylenediaminetetraacetate. Sodium phytate taken orally combines with calcium in the gastrointestinal tract, and thereby its absorption is reduced; it has had only limited success when used in patients with malignancy. The chelating effect of sodium EDTA used intravenously is effective by reducing the ionizable serum calcium in such patients; its prolonged use, however, must be avoided because of its tendency to cause renal tubular damage.²²

SUMMARY

Hypercalcemia was found in 13 per cent of 119 patients with primary carcinoma of the lung. In less than 2 per cent, however, the disconcerting symptoms and signs of the hypercalcemic state became manifest clinically, despite the absence of skeletal metastases. Although skeletal metas-

tases were found in 9 per cent of patients with a normal serum calcium, the finding of an elevated serum calcium raised the probability of skeletal metastasis to 50 per cent. Finally, it is suggested that, when hypercalcemia and malignancy coexist, the height of the serum calcium appears to parallel the biologic activity of the malignancy and may serve as a useful index in ascertaining the effect of therapy directed against the malignant process.

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Choice of Treatment in Spontaneous Pneumothorax

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THE TERM spontaneous pneumothorax has come to be used to describe a pneumothorax that appears suddenly and without warning in an apparently healthy person. There is no accompanying effusion to indicate infection of the pleura. Death from the condition is uncommon and there is, in fact, a remarkable tendency to spontaneous resolution.

The disorder has been known since 1856, when McDowell of Dublin described the case of a young man who suffered with "sudden occurrence of pneumothorax on the left side, arising from the accidental rupture of an air vesicle; dry pleuritis; absence of tuberculous disease; recovery."¹ During this century, the use of x-ray examination of the chest has resulted in an increased awareness of the frequency of the disorder, as well as of its characteristic signs and symptoms. Thus, at present, the sudden, unexpected appearance in a healthy young person of pleuritic chest pain aggravated by change of position, together with a normal or hyperresonant percussion note and decreased breath sounds on examination of the chest, immediately suggests the diagnosis of spontaneous pneumothorax. The chest film is obtained for documentation and for comparison with subsequent films.

The pathologic alteration which leads to the occurrence of spontaneous pneumothorax in an otherwise healthy person is best explained as being due to a ball-valve mechanism acting in a terminal respiratory bronchiole to permit air passage to the alveolus with each inspiration but preventing return of that air with expiration (figure 1). This mechanism was first demonstrated anatomically by Hayashi in 1915, and his finding was later confirmed in a rather extensive study by Kjaergaard.²

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CHOICE OF TREATMENTS

Nature will, without aid, be able to effect a cure of the pneumothorax in the majority of instances by sealing the leak with fibrin and absorbing the air from the pleural space.^{3,4} To allow nature to take its course constitutes an accepted form of treatment. In this method, the physician plays the passive role of an observer, except, perhaps, for an occasional instance when he may perform a thoracentesis to relieve the symptoms of a tension pneumothorax. An alternative method of treatment enlists the active participation of the physician. With this method, pleural air is continuously removed through a catheter with the object of expanding the lung to seal the area of visceral pleural leak against the chest wall. In an uncomplicated case, either of these methods gives a good result. Thus, in most instances, choice of method must be based upon some factor other than the result obtained. It is in this situation that the physician has an opportunity, if not an obligation, to choose the method which restores health at the least cost to the patient.

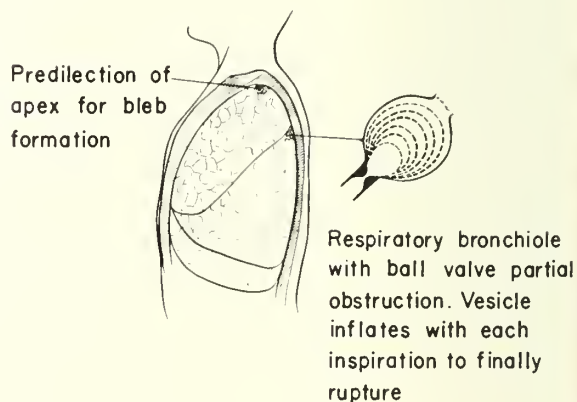


Fig. 1. Pathogenesis of spontaneous pneumothorax. Diagram illustrates common site of pulmonary vesicles and mechanism leading to their rupture. (After Hans Kjaergaard)

TABLE 1

UNSELECTED CASES TREATED WITHOUT CATHETER DRAINAGE BY VARIOUS PHYSICIANS AT A MINNEAPOLIS PRIVATE HOSPITAL

Case	Age	Treatment	No X-rays	Hosp Days	Lung at Discharge	
					Collapsed	Expanded
MK	32	Rest	9	8	✓	
WS	55	Rest	4	19	✓	
RO	32	Rest + 3 taps	4	16	✓	
RK	26	Rest + 1 tap	9	10	✓	
CB	28	Rest	5	7	✓	
LS	34	Rest	1	7	✓	
DP	58	Rest	4	13		✓
CH	32	Rest	4	20	✓	
PH	19	Rest	2	2	✓	
WA	29	Rest + 1 tap	6	4	✓	
PS	62	Rest	3	14	✓	
DH	25	Rest	1	2	✓	
			43 avg	10.1 avg	8.3% expanded at discharge	

MATERIAL AND METHODS

In order to make an intelligent choice between the two methods of treatment, we have compared 3 groups of unselected consecutive cases of spontaneous pneumothorax; 2 groups were treated conservatively—1 at Swedish Hospital, Minneapolis, and 1 at Veterans Administration Hospital, Minneapolis. The patients in these groups were treated by a number of different physicians, but the method was similar—namely, expectant observation plus an occasional thoracentesis. The third group was treated more aggressively and represents our personal experience with consecutive cases seen in private practice over the past three years.

RESULTS

The result of our study of consecutive unselected cases of spontaneous pneumothorax treated in a private hospital by the expectant method is summarized in table 1. It will be noted that the average hospital stay in these cases was 10.1 days. The majority of the patients were discharged from the hospital with some degree of persistent collapse visible on the chest roentgenogram taken nearest the day of discharge. Complete evacuation of the pneumothorax was accomplished in only 8.3 per cent of cases by the time of discharge.

It was not possible to learn the subsequent course of these patients after discharge. We do not, therefore, know the time required for re-expansion of the lung, the number of subsequent visits to the physician's office, the number of additional chest films taken, or when these patients returned to work. It seems reasonable to suppose, however, that those patients whose lungs were not expanded at the time of dis-

charge were advised to continue rest at home for an additional period before they were permitted to return to work. The study of patients treated in a private hospital obviously does not provide a complete picture of spontaneous pneumothorax handled by the expectant method.

To get a better idea of the time required for resolution of a spontaneous pneumothorax when the physician acts the role of a passive observer, we reviewed 15 unselected cases treated primarily by bed rest and an occasional thoracentesis but without catheter drainage at the Minneapolis Veterans Hospital. At this hospital, for various reasons, the practice is to hold the discharge of patients until their treatment is complete. Most of the patients with spontaneous pneumothorax are treated by catheter drainage. However, the policy is not rigid in this regard, and we were able, by review of approximately ten years' experience, to collect for study the records of those 15 patients whose course is summarized in table 2. It should be noted that, even though there is a tendency to hold patients until treatment is completed, only 74 per cent showed complete expansion of the lung by x-ray film at the time of discharge. The remaining 4 patients, however, had only a very slight pneumothorax. The time required to accomplish this result averaged 21.9 days. Since the veterans hospital patients were cured or nearly cured at the time of discharge, we may presume that they were able to return to work immediately.

We now have a clear picture of the course to be expected when we follow the conservative method of treatment. To compare this with the results of a more aggressive attack on the problem, we reviewed our own material over the past three years. Being surgically oriented, we have,

TABLE 2

UNSELECTED CASES TREATED WITHOUT CATHETER DRAINAGE AT THE MINNEAPOLIS VETERANS HOSPITAL

Case	Age	Treatment	No X-rays	Hosp Days	Lung at Discharge	
					Collapsed	Expanded
RK	26	Rest	7	22		✓
JP	21	" 1 tap	5	16		✓
FG	25	" several taps	15	40		✓
HO	29	" " "	5	27		✓
WL	28	" 2 taps	13	23		✓
UN	29	"	6	15		✓
RR	23	" 1 tap	14	42		✓
TA	31	" 1 tap	7	24		✓
HD	34	"	7	23	slight	
JK	32	" 1 tap	13	19		✓
RJ	24	"	4	23		✓
RS	23	" 5 taps	4	10		✓
JL	32	"	7	16	slight	
EC	24	" 1 tap	11	12	"	
RE	22	" 1 tap	6	16	"	
			82 avg	21.9 avg	74% expanded at discharge	

TABLE 3

CONSECUTIVE CASES PERSONALLY TREATED BY CATHETER DRAINAGE AND FOLLOWED AT LEAST SIX MONTHS

Case	Age	Catheter Placed	No X-rays	Hosp Days	Lung at Discharge	
					Collapsed	Expanded
R S	26	Ant	2	3		✓
D A	18	Ant & Apex Post	3	5		✓
A J	38	Ant	3	2		✓
W D	23	Ant & Apex Post	4	7		✓
J B	33	Ant & Apex Post	5	4		✓
P K *	27	Ant & Apex Post	4	3		✓
E T	21	Apex Post	2	1		✓
J M *	68	Apex Post	2	3		✓
F W	17	Apex Post, Ant & Lat	5	5		✓
F M *	63	Apex Post	4	5		✓
H S	30	Apex Post	3	4		✓
G P	40	Apex Post	3	4		✓
G L	30	Apex Post	2	1		✓
			3.2 avg	3.6 avg	100% expanded at discharge	

* 3 cases recurred in 1½ to 3 mo
 Recurrence rate to date 23%

in most instances, when asked to see a patient with a spontaneous pneumothorax, placed a catheter in the chest cavity and connected it to a 3-bottle suction apparatus. The 13 cases in this group are summarized in table 3. Many of these patients were seen by us and treated from the day of their admission to the hospital. In those cases in which we were not asked to see the patient until some days after admission, we have calculated the hospital stay from the time when we first saw him until discharge. This period averaged 3.6 days. It should be noted that all of these patients showed complete evacuation of the pneumothorax by x-ray film at the time of discharge. We have permitted our patients treated with catheter drainage to return to work immediately upon discharge from the hospital. We have, however, advised that they avoid those activities which would cause labored breathing, since this would tend to increase the negative pressure in the pleural space which, theoretically at least, might be undesirable. We do not restrict them from heavy lifting or straining provided that they stop short of that point which causes heavy breathing. All of these patients are, of course, advised to stop smoking from the moment they are seen, with the thought that the chronic bronchitis associated with cigaret smoking may play a part in setting up the ball-valve mechanism which leads to the spontaneous pneumothorax.

We feel that the accelerated rehabilitation of those patients in group 3 is attributable to certain factors of technic which may be worthwhile emphasizing at this point. In the first 6 patients, the catheter was initially placed anteriorly in the second or third interspace, and, as the pneumothorax was evacuated, the lung expanded and sealed itself around the catheter. However, the

air leak, being somewhat removed from the anterior site of the catheter, continued to feed the pleural space in 4 of these cases. Placement of an apical posterior catheter resulted in prompt and complete expansion of the lung and sealing of the visceral leak. We have, therefore, in the last 7 cases, placed the catheter to the apex posteriorly as the initial step and have successfully evacuated the pneumothorax in 6 of these without the aid of additional catheters. The chest x-ray film in case 6 (figure 2) shows one catheter in the anterior second interspace and a second in the posterior third interspace. It is apparent that the posterior catheter must lie near the apex of the upper lobe as well as the superior segment of the lower lobe. Thus the placement of the catheter to the apex posteriorly seems only logical when one considers the predilection of the apex of the upper and lower lobes to bleb formation.

In a patient with a hemopneumothorax, we have had the experience of evacuating the air to seal the lung about the catheter and leaving the blood sequestered at the base and requiring subsequent thoracentesis. If, therefore, we have blood as well as air in the pleural space on the initial chest roentgenogram, we position the patient so that the area of the catheter is depen-



Fig. 2. Anterior catheter enters through second interspace (its tip overlies one arm of the Y connector). The more cephalad catheter enters through the third interspace posteriorly, to be in close proximity to the apex of the upper and lower lobes.

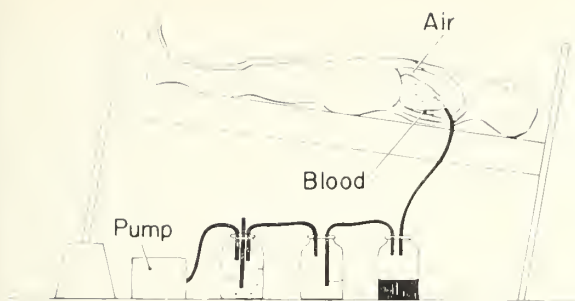


Fig. 3. Spontaneous hemopneumothorax. Before starting suction, patient should be positioned so that blood is evacuated first.

dent before turning on the suction apparatus. This, then, allows for blood to be evacuated first and avoids the need for subsequent thoracentesis (figure 3). We prefer to bring our suction through a 3-bottle apparatus because the parts necessary to construct this apparatus can be found in any hospital and because it provides a

TABLE 4

TREATMENT OF PNEUMOTHORAX FROM AN ECONOMIC VIEWPOINT

Without Catheter Drainage	Avg No X-rays (Cost)	Avg Hosp Days (Cost)	Return to Work	Wages Lost \$ 10.00 / day	Total Cost (\$)
15 VA Hosp cases	8.2 (\$ 57.40)	21.9 (\$ 547.50)	?	\$ 219.00	823.90
12 Private Hosp cases	4.3 (\$ 30.10)	10.1 (\$ 252.50)	?	\$ 101.00	386.60
With Catheter Drainage					
13 Consecutive Personal Cases	3.2 (\$ 22.40)	3.6 (\$ 90.00)	Immed	\$ 36.00	148.00

Summary of cost of treatment with and without catheter drainage, using \$7 as cost of chest film and \$25 as per diem cost of hospitalization.

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CERVICAL DILATION during the midtrimester of pregnancy does not necessarily indicate cervical incompetence and impending abortion. At six months' gestation, 52 of 73 multigravidas had dilation of 1 to 3 cm. and 4 of 27 primigravidas had dilation of 1 cm. None of the 100 patients delivered more than four weeks before term.

W. S. FLOYD: Cervical dilatation in the mid-trimester of pregnancy. Obst. & Gynec. 18:380-381, 1961.

trap bottle for accurate measurement of fluid drainage and a middle bottle containing water through which air evacuated from the chest must bubble and thus demonstrate precisely the end point of air leak. The third bottle provides an accurate yet simple pressure-regulating device.

In table 4, we have compared the two methods of treatment of the initial attack of spontaneous pneumothorax from an economic viewpoint. We have used \$7 as the cost of a chest x-ray film and \$25 as the per diem cost of hospitalization. Our own patients returned to gainful employment immediately upon discharge. We were not able to determine precisely when the patient treated by the conservative method returned to work. We have, therefore, calculated wages lost at \$10 a day for the period of hospitalization only. Comparison of the total cost (table 4) resulting from the two methods of treatment makes it readily apparent that, from an economic point of view, there is much to recommend the active participation by the physician in the treatment of spontaneous pneumothorax. Therefore, assuming that a similar therapeutic result is attained by either the conservative or active method of treatment and considering the difference in cost of the two, we are obligated to choose catheter drainage as the preferred method, providing, of course, that the necessary surgical skill is available.

SUMMARY

We have compared the cost of hospitalization for pneumothorax when treated by the expectant method of observation and occasional thoracentesis with that of the active method using catheter drainage. We have discussed briefly some important technical features of the latter method. We have concluded that the physician is obligated, from the standpoint of economic saving, to use the active form of therapy whenever surgical help is available.

Natural History of Colorado Tick Fever Virus

CARL M. EKLUND, M.D.

Hamilton, Montana

OVER 100 VIRUSES have been isolated from arthropods, such as mosquitoes, ticks, *Culicoides*, and *Phlebotomus*. Approximately 30 have been shown to cause disease in man and in his domestic animals. The essential virus cycle for the maintenance of most of these viruses is found in nature, and man or his domestic animals are usually only accidentally infected; but the study of these cycles has proved difficult. The purpose of this presentation is to illustrate the methods used in the study of the natural history of such viruses. Since a reasonably clear picture of virus maintenance has been obtained only with respect to the tick-transmitted viruses, a brief summary will be given of work done at the Rocky Mountain Laboratory on the maintenance of a tick-transmitted virus, that of Colorado tick fever.

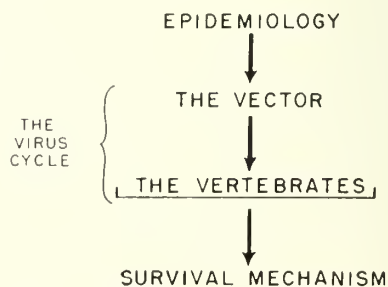
PROCEDURE

Figure 1 outlines briefly the method of investigating the ecology of an arthropod virus. The starting point is disease. The geographic and seasonal occurrences of the disease and the age, sex, and occupation of affected persons point to a particular arthropod vector. When this arthropod has been further established as a vector by repeated isolation of virus, the hosts on which the arthropod feeds are studied. It is necessary to show that these hosts, when inoculated with virus, have a viremia sufficient to infect the arthropod and that an arthropod-host-arthropod virus cycle can be established in the laboratory. Following this, virus must be isolated from the host animals in nature frequently enough so that it can be concluded that they play an important role.

Since Colorado tick fever usually has a typical dengue-like, diphasic, febrile course with marked clinical grounds. Virus can be easily isolated from the blood of patients. Therefore, the first step in the investigation, the establishment of a clinical entity, is readily accomplished. At the Rocky

Mountain Laboratory, virus has been isolated from the blood of over 650 patients. The important epidemiologic findings concerning this group are: (1) all 650 persons lived in the western mountainous region of the United States just prior to onset (figure 2); (2) all were in the area at a time when ticks are active (figure 3) and they had engaged in activities—such as tending stock, working in the forests, camping out, or fishing—which brought them in contact with ticks; and (3) many gave a definite history of tick bite. The only tick which fits the geographic distribution of cases and commonly feeds on man is *Dermacentor andersoni*, which is a 3-host tick. It must engorge on blood as a larva, a nymph, and an adult. After taking blood, it drops off the host and molts to the next stage and then must find a new host. Virus is readily isolated from *D. andersoni*, and the incidence of infected ticks is commonly 10 per cent or higher. The incidence is higher in well-watered mountainous areas than in arid sagebrush areas, as shown in the table. This difference in incidence appears to be related to the numbers of small and large mammals which serve as hosts for the various stages of the tick. Virus has been isolated from the hosts on which the larvae and nymphs feed, such as chipmunks, golden mantled and Columbian ground squirrels, pine squirrels, porcupines, and white-footed mice. In the laboratory, it has been

A CHARACTERISTIC DISEASE PICTURE



COLD OR DRY PERIODS UNFAVORABLE FOR THE VECTOR

Fig. 1. Ecologic study of an arthropod-transmitted virus

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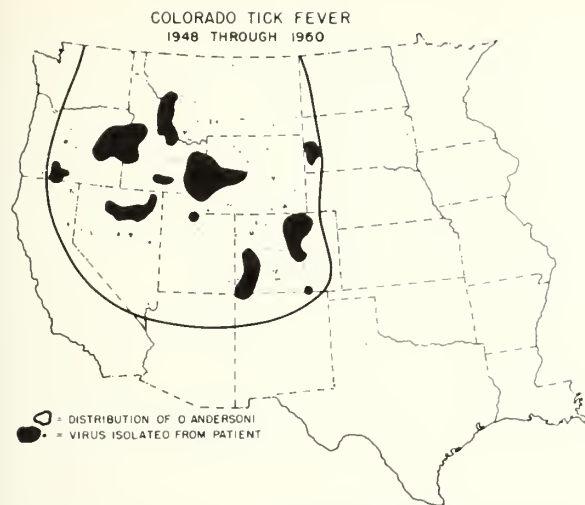


Fig. 2. Comparison of the distribution of 650 human cases of Colorado tick fever with that of *D. andersoni*

shown that following inoculation of Colorado tick fever virus, such animals have a symptomless infection characterized by viremia of many days' duration and that larvae and nymphs become infected by feeding on them. Virus has also been isolated from engorged larvae and nymphs found on these animals in nature.

These observations provide definite evidence of a virus cycle involving larvae and nymphs and small mammals. The question of the role of adults in the maintenance of virus is raised because it has long been known that spotted fever rickettsiae pass from one generation of tick to the next through the egg. Also Russian and Czechoslovakian workers have reported that similar transmission of Russian spring-summer encephalitis virus occurs in ixodid ticks. We have not been able to obtain evidence of transovarial transmission by ticks infected in the laboratory or in nature, but we have shown that virus

INCIDENCE OF COLORADO TICK FEVER INFECTION IN
DERMACENTOR ANDERSONI AS RELATED TO
TYPE OF LOCALITY

State and year	Arid		Well-watered	
	No. ticks	No. isolations	No. ticks	No. isolations
Nevada, 1952	1198*	4	2205	63
Washington and Idaho, 1954	1173	1	1381	44
Montana, 1954 and 1955	1732	1	1902	37

*Usually examined in pools of 20 ticks

passes from stage to stage in the development of the ticks.

Our concept of the maintenance of Colorado tick fever based on the foregoing observations is illustrated in figure 4. A nymph carries virus through the winter and in the following spring or summer feeds on a small mammal. Viremia results and larvae feeding at the same time become infected, molt to nymphs, and, in their turn, carry virus through the winter. Adult ticks play some role in the maintenance of the virus, for all 3 stages in the development of the tick

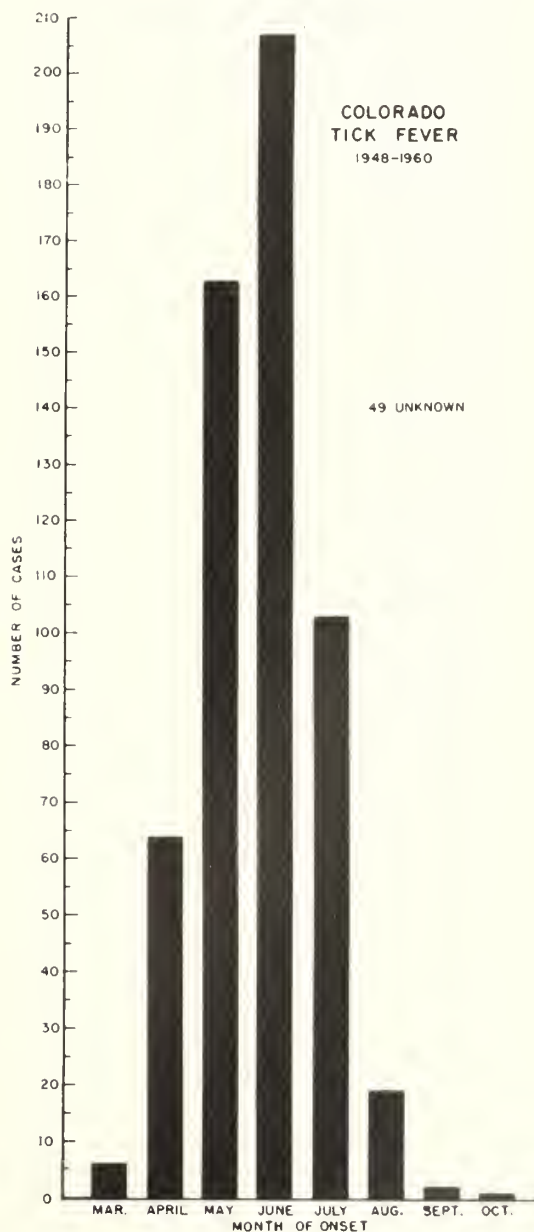


Fig. 3
Seasonal occurrence of Colorado tick fever in man

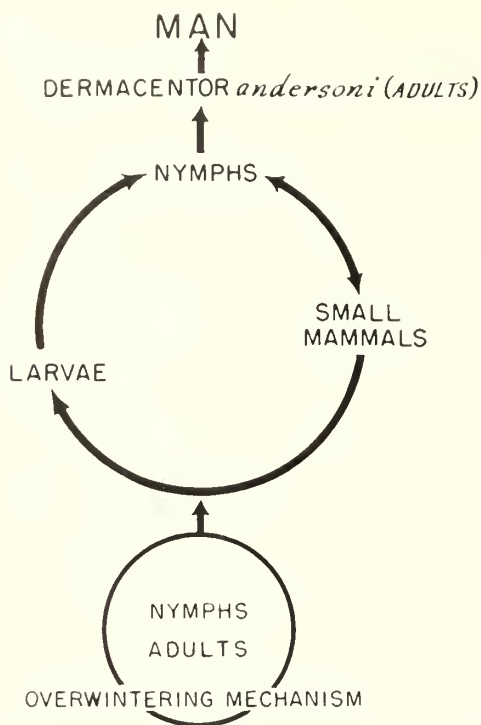


Fig. 4. Ecology of Colorado tick fever virus, diphasic febrile disease with leukopenia

may feed on animals the size of a porcupine. Such an animal can be infected by the adult tick, and larvae and nymphs feeding at the same time are infected.

This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.

The cycle of infection involving small mammals, larvae, and nymphs of *D. andersoni* represents the main stream of infection, but there are probably side eddies of infection, since virus has been isolated from the following tick species: *D. parumapterus*, *D. occidentalis*, *D. albipictus*, *Haemaphysalis leporis-palustris*, and *Otobius lagophilus*. These species do not, however, have the geographic distribution or feeding habits necessary to account for human infection.

SIGNIFICANCE OF FINDINGS

What significance do these findings have as far as control of Colorado tick fever infection in man is concerned? The areas which support the virus cycle are so large and the character of the terrain is such that eradication of the virus through destruction of the tick or its hosts is impossible. Insecticides can be used to control the tick population in restricted areas, such as camp sites and along frequently used trails. Tick repellents are efficacious and these, together with the use of proper clothes, can greatly reduce tick exposure. Development of a vaccine from infected suckling-mouse brain has been progressing favorably, and this vaccine may have limited use in protecting individuals who must work in tick-infected areas for long periods.

This report represents collaborative work of many individuals, particularly Richard Kennedy, Glen Kohls, Willy Burgdorfer, Carleton Clifford, and Leo Thomas.

DIRECT ANATOMIC communications exist in dogs between lymph nodes and venous channels, exclusive of efferent lymphatic ducts. When lymph nodes are injected first with 1 or 2 cc. of saline and then with air, air bubbles can be seen to enter directly into the vascular system. Only moderate digital pressure upon the syringe produces immediate air displacement in the adjacent vascular channels of the cervical lymph node, with bubbles grossly visible within veins emerging directly from the gland as well as within communicating veins and the principal regional veins of the neck. As digital pressure is released, veins gradually refill with blood. Efferent lymphatic channels emerging from the lower pole of the cervical node also fill with air bubbles so that air enters the venous and efferent lymphatic channels simultaneously. Occasionally, however, veins fill without air entering efferent lymph ducts.

J. J. PRESSMAN and M. B. SIMON: Experimental evidence of direct communications between lymph nodes and veins. *Surg., Gynec. & Obst.* 113:537-541, 1961.

Occult Hypothyroidism with Cardiomegaly

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THIRTY-SEVEN YEARS AGO, on January 31, 1925, the first publication written in the English language on myxedema heart appeared in this country in the *Journal of the American Medical Association*. The author was Dr. George E. Fahr.¹ He described 2 cases in detail, one of them having been diagnosed in 1923. Only five years earlier, in 1918, the first case of myxedema heart ever described was presented by Zondek² in the German literature. At that time, most authors, in discussing myxedema, neither mentioned nor connected it directly with any form of heart disease.

By 1927, Fahr³ published another paper in the *American Heart Journal* in which he reported 6 cases. This article was followed by further studies and contributions to the literature on the subject.⁴

Over the past thirty-five years, Fahr has been continuously interested in this problem. At present, whenever one reviews any article on myxedema heart, one constantly notes references to his authority in this particular field.

REVIEW OF PERTINENT LITERATURE

The classic findings of hypothyroidism with associated heart disease are well known. Usually, myxedema heart is seen only in prolonged, severe hypothyroidism.⁵ Clinically, besides the general symptoms and findings of myxedema, the cardiac features are variable. Any degree of congestive failure may be present. The heart size is diffusely increased and there may be difficulty in feeling the apex beat. Cardiac sounds are muffled, and the rate is usually slow.

The electrocardiogram reveals generalized low voltage in all the limb leads with flattening or negativity of the T waves. Fluoroscopy suggests a globular, "sluggish" heart, and on roentgenograms the silhouette size is increased on both the right and left sides. The globular shadow is due to cardiomegaly or pericardial fluid or varying degrees of both. The basal metabolic rates are usually below -25 per cent. The blood cholesterol is high, over 250 mg. per cent; the pro-

tein-bound iodine and thyroid radioactive iodine uptake are below the lower limits of normal, which are 4 μ g. per cent and 15 per cent, respectively.

Autopsy specimens showing cardiac pathology are not numerous. Those available reveal pericardial effusion, ventricular dilatation, and hypertrophy. Microscopically, one may see interstitial edema and swelling of myocardial fibers with some replacement of the sarcoplasm by a basophilic material.⁶

Apparently there is a great variability in the hypothyroid syndrome. Some patients may have the classic picture. Others may show primarily mental, emotional, and neurologic aberrations and minimal metabolic abnormalities. Others may have mainly skin or metabolic changes, and still others may have predominantly cardiac findings.

In one of his early reports, Fahr states, "I have seen one case of what I believe to be very mild myxedema with mild cardiac symptoms including slight dilatation of the heart as determined by teleroentgenography with a basal metabolic rate of -12 per cent in which the cardiac symptoms apparently responded to thyroid medication after digitalis failed to make any impression on the symptoms of myocardial insufficiency."¹

Recent research work on the thyroid hormones and their synthetic analogues seems to suggest that there is a separation of their effects.⁷ Some work slower and longer; others affect only the cholesterol but not the basal metabolic rate, or vice versa. Size of the dose of thyroid hormone can cause a differential effect; that is, a small dose can lower the cholesterol but not change the basal metabolic rate.

In pretibial myxedema, in which oral therapy does not affect the skin, the local injection of triiodothyronine causes a reversal to normal structure grossly and microscopically.⁸ This all suggests that the various thyroid hormones and their analogues may achieve separate differential results quantitatively and qualitatively.

Clinically, gynecologists have noted that thyroid will often convert metrorrhagia to normal menses in spite of a normal basal metabolic rate. Often, one sees very obese women with infrequent menses who have a normal basal metabolic

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rate. Thyroid will produce normal menses with very little change in the metabolism.

An additional note of clinical interest is that striking changes in the electroencephalogram of patients with hypothyroidism can be demonstrated even in the absence of significant clinical abnormalities.⁹

CASE REPORT

At this time, I should like to present a case in which the manifestations are primarily related to the cardiac silhouette.

The patient is a 57-year-old white woman, whom I first saw in 1951 for a routine examination. At that time, the history and physical examination revealed no significant abnormalities. No findings of hypothyroidism were noted. The patient was an alert, cooperative, intelligent, vigorous woman who attended dancing classes and had no disability. Her hair and skin were delicate and fine rather than coarse. Instead of being lethargic, she was slightly nervous and complained more of hot flashes than of being cold.

The routine blood test and urinalysis were normal. Serologic test for syphilis was negative and her sedimentation rate was normal. The electrocardiogram was normal, and the chest film made in 1951 revealed no unusual findings (figure 1). The cardiac silhouette had a transverse diameter of 14.5 cm., which was approximately 50 per cent of her transverse thoracic diameter.

In 1952, the patient was in the hospital for removal of a benign lesion of the breast. At this time the radiologist

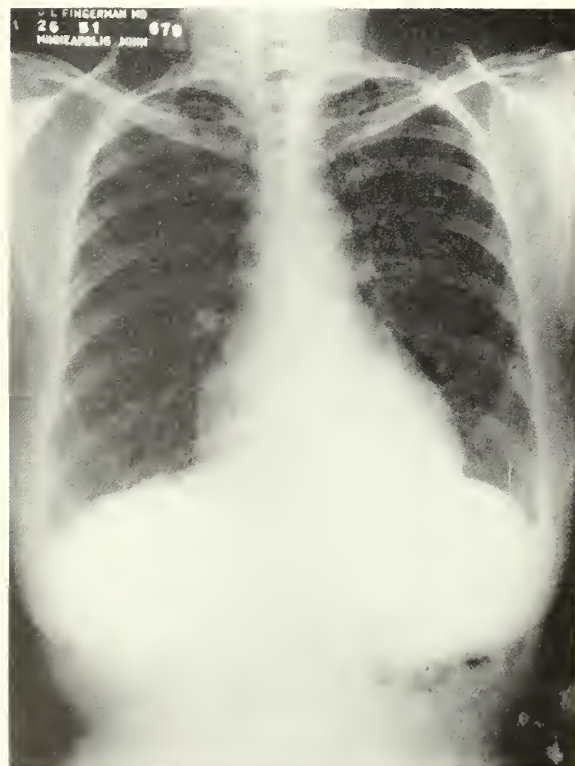


Fig. 1. Normal chest roentgenogram made in 1951



Fig. 2. Chest roentgenogram made in 1959. Note striking enlargement of cardiac silhouette.

reported, "The heart is slightly enlarged in its transverse diameter. The appearance suggests generalized cardiac enlargement." This film is no longer available for study.

In 1956, during a routine examination, another chest film again suggested generalized cardiac enlargement. The transverse cardiac diameter was now 15.5 cm. No new symptoms or findings were elicited. Particular attention was directed to the cardiovascular system. No chest pain, dyspnea, murmurs, or other abnormalities were discovered. The blood pressures were between 130/80 and 150/90. The electrocardiogram showed slightly lowered voltage but was otherwise normal. At this time, the cholesterol was 214 mg. per cent.

In March 1959, the patient was again studied. Enlargement of the cardiac silhouette had become quite striking on both the right and left sides (figure 2). Even at this examination, significant complaints or physical findings were totally absent. The transverse cardiac diameter was 16.5 cm. The electrocardiogram had even lower voltage in the limb leads; T_1 had become almost flat, and T_{av1} had changed from positive to diphasic.

Radio iodine uptake was 19 per cent. The protein-bound iodine was 4.3 μ g. per cent. Blood cholesterol readings were 250 and 204 mg. per cent. Results of 3 basal metabolic rate tests were -7, -23, and -20 per cent.

These tests did not seem to provide the answer to the problem, since the results were mainly within the lower range of normal limits, although they were below the average mean. And it was assumed that, in order to have a myxedema heart, one must have, as the literature states, "prolonged severe hypothyroidism."

After fluoroscopic study of the patient, the radiologist stated, "The cardiac pulsations appeared somewhat diminished in amplitude along the cardiac border." A film

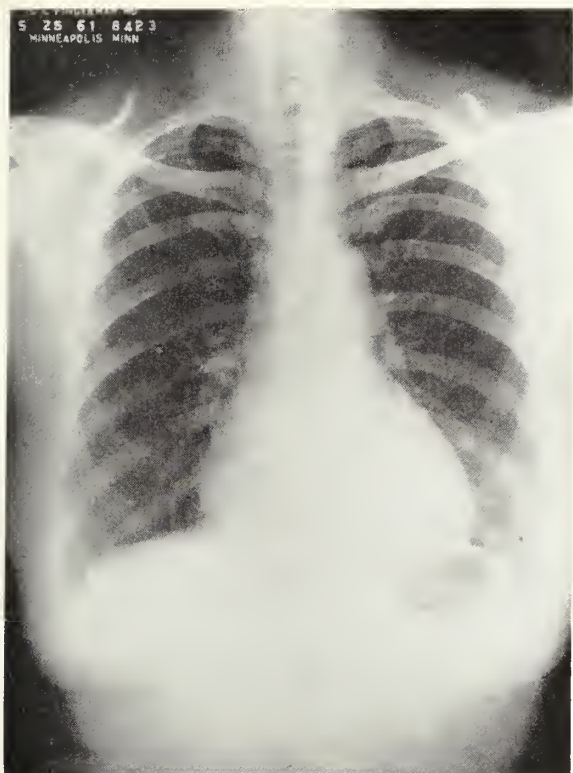


Fig. 3. Chest roentgenogram made in 1961. Cardiac silhouette is similar to that seen in 1951 film.

obtained in the supine view showed no significant change in cardiac configuration compared with the upright view.

A comparison of all the films available since 1951 showed a progressive, generalized enlargement of the cardiac silhouette. No gross evidence for a pericardial effusion was found, and the reason for the enlargement was not apparent in the roentgenograms, according to the radiologist.

Dr. Leo Rigler, who was kind enough to review the films, stated, "The flask shape is strongly suggestive of myxedema heart and lesions other than myxedema which might produce the same picture. It certainly does not correspond to the usual hypertensive or valvular heart disease."

In April 1959, the patient was started on small doses of thyroid extract, and dosage was gradually increased. Great caution was taken since it was felt that all types of cardiac enlargement other than myxedema heart would likely be aggravated by this therapy. As time went by, the size of the cardiac silhouette gradually decreased, until by 1961 it became quite similar to that seen ten years previously in 1951 (figure 3).

It should be noted that, after this period of therapy, the cholesterol was 215 mg. per cent. The basal metabo-

lic rate was $+3$ and $+7$ per cent, and the electrocardiogram reverted to the configuration seen in 1951.

SUMMARY AND CONCLUSION

A case of gradual progressive enlargement of the cardiac silhouette over eight years is presented.

During this time, no other significant abnormalities associated with hypothyroidism were discovered. The metabolic studies were mainly within the normal range, although below the average mean. No significant symptoms or physical findings suggested hypothyroidism.

Desiccated thyroid was given over a period of two years, and, simultaneously, a decrease in the cardiac silhouette to the size seen in 1951 was apparent.

The impressions gained from this ten-year study are that this case represents a forme fruste or occult type of myxedema heart disease and that myxedema heart disease is not necessarily associated with prolonged, severe hypothyroidism. Perhaps, occasionally, other cases of so-called idiopathic cardiomegaly might be this form of myxedema heart. This concept is also consistent with current attitudes regarding the marked variability in the types of hypothyroidism and the variabilities in response to thyroid hormones and their analogues.

The author wishes to express his gratitude to Dr. Alvin Schultz and Mrs. Harriett Fingerman for their suggestions and effort in the preparation of this report.

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This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.

The Changing Approach to Myocardial Infarction, 1927-1962

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IN 1927, I first began to work under Dr. George Fahr. Since then, much has happened in the fields of medicine, and I thought it might be useful to trace the course of one rather common disease during that period.

In 1900, Dr. John Rothrock reported a case of thrombosis of a coronary artery with myocardial infarction to the Minnesota Academy of Medicine.¹ This was ten years before any known report on this disease appeared in the literature. Obrastzow and Straschesko² first described the clinical entity of coronary thrombosis in the literature in 1910. In 1912, Dr. John Herrick³ more completely discussed this entity in the American medical literature, and, in 1919,⁴ he reported the case of a physician who died of this disease and whose electrocardiograms showed a pattern similar to that found in dogs with ligated coronary arteries. Postmortem examination revealed a lesion resembling those found in the same dogs.

It is interesting to examine the text books of that day. In *Outlines of Pathology*, published in December 1924, Dr. E. T. Bell admits there is such a thing as coronary sclerosis with arteriosclerosis in the coronary artery. Here is a quotation from that volume: "In some instances death is caused by the formation of a thrombus in the diseased artery. Occasionally coronary thrombosis brings on an attack of acute epigastric pain which is mistaken clinically for perforated ulcer." In the eighth edition of *The Principles and Practices of Medicine*, by Sir William Osler, published in 1918 and written with the assistance of Thomas McCrae, coronary thrombosis is not mentioned, but angina pectoris is well recognized. In their tenth edition published in 1925, the same authors discussed coronary thrombosis and admitted it did occur, particularly in middle-aged or elderly persons. By 1934, John Musser, in his *Textbook of Internal Medicine*, had an extensive section on coronary thrombosis which revealed he had a good insight into the problem.

In the early years covered by this paper, coronary thrombosis was not nearly as much stressed as was coronary sclerosis with narrowing and scarring of the myocardium as a result of sclerosis. We know now that much of this scarring was caused by small thrombotic episodes, but it was previously believed that a great deal of this difficulty was the result of narrowing of coronary arteries alone and not of any direct closure. I remember a patient admitted to Minneapolis General Hospital in 1931 with a board-like abdomen; an electrocardiogram showed acute changes. I can still vividly remember running to the operating room to tell the surgeons that this patient should not be operated upon because he had a coronary thrombosis. I can just as vividly remember having been physically ejected from the surgery department for even intimating an abdominal condition could be the result of a myocardial infarction. Subsequent events proved that the patient did have a myocardial infarction with no evidence of any abdominal condition. This was not an isolated instance but was the normal reaction of physicians of the day, many of whom were scarcely aware that coronary thrombosis with myocardial infarctions could occur.

Since that time, the first major advance has been a better and more orderly diagnosis of this condition. Certainly, our knowledge of the disease has led us to be more perceptive of the history involved, and we can now make this diagnosis with considerable accuracy by the history alone. In addition to our improved interpretation of electrocardiograms, the more extensive use of these tracings and the extension to more leads than were used in 1930 have enabled us to be much more accurate in our diagnosis of small changes in the myocardium. Consequently, today, we are diagnosing smaller infarctions than we did previously, and to some extent this is reflected in the increased incidence which is being reported.

Over a period of years, we have learned that this disease is accompanied by increased white

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blood count and sedimentation rate, fever, and often excretion of urobilinogen in the urine. Later, the transaminase test became popular, and, although not specific, this test does provide strong support for the diagnosis of myocardial necrosis when other conditions which would produce transaminase rise are ruled out.

The treatment of this disease has also evolved over this period of years. At first, the only treatment was morphine with bed rest; if the patient turned blue, he was given oxygen, and, if dyspnea developed, he was digitalized. Experimental work showed that dogs with artificially induced infarctions had a better survival rate if papaverine, atropine, morphine, or quinidine was given in adequate doses. Papaverine decreases blood vessel spasm; although the occluded artery is no longer in spasm, there is secondary spasm of other coronary arteries and arteries in the pulmonary system. Atropine serves the same purpose and is used by many. Morphine is still best for controlling pain because it also allays anxiety, an action which in itself is helpful in treatment of the disease. The prophylactic use of quinidine was recommended for many years, but its use is now on the decline. Most physicians reserve quinidine for patients who have already shown some signs of arrhythmia. It was also demonstrated that decreasing the caloric intake decreased the metabolic rate, and, inasmuch as the work of the heart is directly related to the oxygen consumed, decrease in metabolic rate is advisable. The danger of shock has been eased with the use of pressor drugs such as norepinephrine (Levophed), which have the ability to raise the blood pressure.

The major step forward in the last decade has been the use of the anticoagulant drugs, which decrease the tendency toward thromboembolic episodes subsequent to coronary occlusion. These drugs also reduce the possibility of the thrombus propagating and hence involving other branches of a given coronary artery. Long-term use of anticoagulant drugs is routinely practiced by many physicians today to prevent some of the recurrences of coronary thrombosis. Although the statistical advantage is small, such prophylactic treatment is warranted provided the person can be maintained on anticoagulant therapy without too many side effects. Our personal experience with patients receiving long-term drugs of this kind shows few difficulties involved. Our experience also reveals that there will always be a certain number of patients who have new myocardial infarctions despite adequate anticoagulant drug dosage.

Now that we physicians have learned to

make the diagnosis of coronary thrombosis and have evolved an adequate therapy for the acute condition, we should concern ourselves with the causes of this disease, which in turn will lead us to consideration of prevention. I am impressed with the fact that, whenever we are faced with a new disease and have very little information as to causation, we seem to be unconsciously motivated by the phrase, "The wages of sin are death." This sometimes encourages us to seek the cause of a new disease in certain phases of living which are usually considered pleasurable but, in the eyes of some, sinful—eating, drinking, smoking, and sexual activity. Eating to sustain life is acceptable; overeating is gluttony. A sign of overeating, of course, is increased body weight, and this is not acceptable from a moral and religious standpoint. The same thing is true of drinking alcoholic beverages, but here the prohibition is even more stringent. Smoking too has been condemned and in the eyes of many is deleterious physically and a sign of moral decay. All of us are familiar with the taboos surrounding sexual activity. So here around the acts of eating, drinking, smoking, and procreation we have a social environment which indicts them generally and specifically in the case of excess, overindulgence, or any deviation from the socially acceptable pattern of behavior. The so-called "virtuous" acts of life are almost never indicted as being possible causations for disease; it is always those practices which do not enjoy the community's approbation.

At this time, the cause of coronary thrombosis or coronary disease is not known despite all the investigation. I recognize that there has been a great amount of work done in the field of fat metabolism and that extensive epidemiologic studies have been made relative to it. I can see no present proof that coronary disease is directly related to any specific item in our diet and no positive evidence to show that the elimination of any item has increased the longevity of any given individual. No proof exists today that excitement or nervous tension has produced this disease, although many persons would like to link coronary thrombosis to that cause. Smoking has been indicted but only in very nonspecific statistical terms; no one has yet shown a direct relationship between smoking and its effect on the individual or the causation of a coronary thrombosis.

The way to prevent coronary disease is not known. Those who are strong proponents of the fat factor as a cause of coronary arteriosclerosis would have us all on diets of low-fat intake. As I have said before, there is as yet no proof that

changing to a low-fat diet has any bearing on the longevity of any given individual. Only time will tell, and many complex investigations are needed to establish whether the avoidance of fat in the diet or changing to unsaturated fats will increase the longevity of any group of persons. Although smoking has been cited as a primary cause by some researchers, no proof exists that cessation of smoking has anything to do with increasing the length of life by preventing the development of arteriosclerosis; neither has the avoidance of increased nervous tension proved to be of any value.

Some physicians believe that we do not exercise enough and that, if we would increase our exercise requirements, we would have a better chance to live longer. I will grant there is some evidence that increased exercise does add to the ability of our hearts to do work. Whether this is by reason of increased muscular tone or the result of less coronary arteriosclerosis or more collateral circulation is debatable.

Statistically, our inheritance would seem to play a role. Families with a history of many members with atherosclerosis will produce offspring who will have a higher chance of having coronary disease. It would be helpful if many of us could change the hereditary characteristics with which we were endowed, but unfortunately we cannot. Possibly, in the future, we will be able to inhibit the propagation of certain of the "bad characteristics" which would otherwise be transmitted to our offspring.

The long-term use of anticoagulant drugs has already been discussed. Presently, it lends a statistical advantage to individuals, although one could not safely advise all persons more than 40 years old to begin taking anticoagulant drugs. I understand this is being done by a physician in Boston; it will be interesting to see what his statistics are over the next twenty years.

Opinions of the prognosis of coronary thrombosis have changed considerably. Originally, this was thought to be a fatal disease and, although occasionally a patient would live for five to seven years after the attack, it was considered remarkable if the person would survive a year or so. Now, because of better care, more accurate diagnosis of small lesions, or some other unknown reason, the prognosis has improved. Several years ago, the average life expectancy was seven years provided the patient lived past the first twenty-four hours. Today, it is not unusual to see patients alive ten to fifteen years after the coronary thrombosis occurred and still doing extremely well. Formerly, it was thought patients should not go back to work, but our ideas on this are

also changing very rapidly. Entirely new approaches are being taken to these patients as far as their work ability; a promising one is an improved method of evaluating ability to work.

Nearly all patients with coronary thrombosis will recover from an acute attack, and we know that most of them subsequently will have a fairly good functioning myocardium. The problem then is to determine which of these patients can go back to their former vocations and carry on a normal life. Previously, this was handled by saying the patient should go back to light or sedentary work or possibly he could do moderately heavy work, but, up until the last few years, no one made a very exact attempt to determine what the work ability would be after coronary thrombosis. In Minnesota, we have been using a work classification unit to determine the work potential of a given patient.

I realize that many physicians older than I, and some of the younger ones, feel that a person who has had a coronary thrombosis should never work again. Recently, I was shocked to hear a physician say that he frankly told his patients with coronary occlusions they should never work again, even in such light work as dentistry. Those of us who assist in work classification units know this is not the case. I recently startled several hundred physicians when I told them that in the work classification unit we have used the double Master 2-step test on 75 per cent of the patients who have come to our unit after having myocardial infarction. We encountered no serious incident. It is true we excluded persons with status anginosus or cardiac failure and did not do this test until three months after the infarction. At that point, however, if the patient has no acute symptoms, we believe it is feasible to test his work ability. The double Master 2-step test requires an output of approximately 8.5 calories per minute. This is a fairly heavy output and, contrasted to most requirements in industry, would correspond to what we call heavy work. To be sure, there are jobs with higher requirements, such as sawing hard wood, lifting 100 lb. up a ladder, or driving a wedge with a maul, but most of the occupations we engage in today have energy requirements much lower than that of the double Master 2-step test. Our practice has been to have all patients attempt this test. If pain and shortness of breath develop, the test is stopped. If we have any suspicions at all that a patient may have a rather poor work capacity, we do the single Master test and make an electrocardiogram. If no pain, shortness of breath, or electrocardiographic changes develop, we are willing to do the double Master test: 40 steps

over the 2-step apparatus within three minutes. If, during that period of time, the patient has had no pain or shortness of breath and no change is seen in the post-exercise electrocardiogram, we believe he can safely do work up to this level of 8.5 calories per minute without any injury to the myocardium.

It can be argued that three minutes is a short period of time. However, it has been shown that, at three minutes, a plateau has already been reached and that this value will hold for a long period of time thereafter. In other words, if a patient can do this much work for three minutes, the chances are excellent that he can do it for several hours at a time. Today, we know the work requirements of most vocations. The tasks we consider medium heavy work require 3.5 to 4 calories per minute. Obviously, persons who can do work at 8.5 calories per minute can easily manage tasks requiring 4.5 calories per minute. A very high percentage of the patients we have tested are able to do the double Master 2-step test without difficulty. This would have been considered shocking ten to twenty years ago, but,

at the present time, those of us who engage in this type of work take such rigorous testing in stride.

To recapitulate, our attitudes and approaches toward coronary thrombosis are continually changing. We are now at the stage where we are still attempting to find the cause, are searching for ways of preventing the disease, have improved our diagnostic and treatment skills, and have developed better tools to measure the patient's ability to work. Although myocardial infarction is a serious disease, we have learned to face it optimistically, for we know that a great majority of its victims will survive, recuperate, and eventually become useful, productive citizens with a reasonably good life span.

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This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.

TRANSIENT benign enlargement of the breast is common in adolescent boys, usually disappearing within one to two years without treatment. Malignancy in the adolescent male breast is nonexistent or extremely rare, and no other ill effects have been observed. Occurrence and degree of enlargement appear to be positively correlated with size of testes, thyroid, and penis and with amount of pubic hair, but not with axillary, facial, trunk, body, or extremity hair. The incidence is less among Negro boys.

Management is usually limited to observation, without surgical or hormonal treatment, though both boys and parents should be assured that adolescent gynecomastia is normal and transient. Operation is needed only for extreme prominence of the breasts constituting a psychologic handicap. The procedure is simple removal of the subareolar breast tissue, saving the nipple and areola, since emotional disturbances can follow mastectomy.

A total of 2,369 physical examinations were performed for 1,890 presumably normal boys, aged 10 to 16 or slightly older, in a Boy Scout camp; all obese boys and those of unknown age were excluded, leaving 1,855 examinations for analysis. Incidence of gynecomastia was 38.7 per cent, with a peak incidence of 64.6 per cent in boys 14 to 14½ years. Enlargement was unilateral in 23.3 per cent—right in 15.2 per cent and left in about 8 per cent. Of 173 boys given two annual examinations, 24 per cent had subareolar nodules on both occasions; of 52 examined three years, 36.5 per cent had nodules twice and only 7.7 per cent three times.

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Ralph Leland West, D.V.M.

*Guardian of the Health, Welfare,
and Longevity of Man and His
Domestic Animals*

J. ARTHUR MYERS, M.D.

Minneapolis

LOVE OF THE LAND, animals, and the outdoor life is not a rarity for Minnesotans, but when one native son, Ralph Leland West, D.V.M., was the first one in his family to choose to become a farmer, this indeed was unusual. Both his parents were native Minnesotans, as all four of his grandparents arrived and settled in Minnesota during territorial days before his parents' birth. The men of the family had all favored careers as educators, doctors, and businessmen.

It was in Faribault, Minnesota, on June 6, 1888, that the fourth child, Ralph Leland West, was born to Mr. and Mrs. Willis Mason West. His father, a graduate of the University of Minnesota in 1878, was later head of the Department of History at the University for many years and author of a number of textbooks on ancient, modern, and American history.

The family came to Minneapolis to live, and here Dr. West received his elementary and high school education. He graduated from the College of Agriculture at the University of Minnesota with a Bachelor of Science degree in mid-year 1909 at the age of 20, having completed the four-year course in three and a half years. While attending the university, he majored in animal husbandry, and he attained membership on both the livestock and dairy-stock judging teams in 1908.

Filled with enthusiasm and the necessary educational background, young Ralph was now ready to begin his life as a farmer. This he pursued successfully for several years in Minnesota and North Dakota until his health halted his farming career. Undaunted by this setback, he turned to his interest

in livestock and decided to make working among animals his goal. He matriculated in Kansas City Veterinary College at Kansas City, Missouri, graduating with a degree of Doctor of Veterinary Medicine in 1918.

What Dr. West lost in being unable to carry out his desire to be a farmer, Minnesota and the whole country gained from his accomplishments during his long term of office as secretary and executive officer of the State Livestock Sanitary Board, to which he was appointed February 15, 1942. He held this position until he was retired from the state service December 31, 1959. He served nearly eighteen years as the chief livestock sanitary officer of the state.

Upon graduation, Dr. West was called into active service in the Veterinary Corps of the army and, upon discharge at the end of the war, he established a practice in general veterinary medicine at Waseca, Minnesota. There he conducted a successful practice until February 15, 1941, when he accepted employment with the State Livestock Sanitary Board and moved to St. Paul. The following year, he succeeded Dr. Charles E. Cotton, who had retired.

Dr. West had married Miss Elsie Wardall of Grand Rapids, Minnesota, in 1912, and the couple have 5 children: 3 sons and 2 daughters. Two of the sons, Leland and Daniel, are now partners in the veterinary practice established by their father at Waseca.

AFFILIATIONS

The high honors that have come to Dr. West for his accomplishments are easily understood by a brief glance at his active life. His interest in public affairs

began as early as 1910, when he was only 21 years old and helped organize Harris Township in Itasca County, serving as the first town clerk. He was a member of the Board of Education in Waseca for many years and served as president. He was on the town's City Council until he left for St. Paul. Dr. West has always been active in organizational work in his professional life, always willing to lend his support and efforts to any project that would benefit mankind as well as animals. In 1924, he was elected president of the Minnesota State Veterinary Medical Association and served as a member of the Board of Trustees of the organization for a number of terms. He has been a member of the Executive Board and vice-president of the American Veterinary Medical Association. He helped organize and served as president of the Southern Minnesota Veterinary Medical Association.

During his work on disease control with the State Livestock Sanitary Board, Dr. West served as president of the National Assembly of Chief Livestock Sanitary officials, as president of the United States Livestock Sanitary Association, and as head of the association of Chief Livestock Sanitary Officials of the North Central States. He has served on many important committees of the United States Livestock Sanitary Association. For many years, he has been on the committees on tuberculosis and on brucellosis as chairman and member. He has also served on the committees on rabies and on laws and regulations, and, for several years, he was chairman of the committee on legislation.

As chief sanitary official, Dr. West has always worked closely with other state departments, particularly the Department of Health. He has been a dedicated worker in stressing the necessity of eradicating diseases of domestic animals which may be transmitted to human beings, such as rabies, ornithosis, tuberculosis, and brucellosis.

He has long been active in the affairs of the Minnesota Public Health Conference and, on September 24, 1959, was elected to honorary membership in the organization. He has served as an ex officio member of the Water Pollution Control Board from the time of its establishment by the legislature in 1943 until his recent retirement. He has been vice-chairman of the group for the last several years. He has served as a member of the Executive Committee of the Minnesota Tuberculosis and Health Association.

Dr. West has the distinction of being the first veterinarian to be appointed a member of the advisory committee to the United States Secretary of Agriculture on Dairy Marketing and Research. He was appointed in 1954 and still serves on the committee.

ACHIEVEMENTS ON LIVESTOCK BOARD

The Minnesota Livestock Sanitary Board has been awarded recognition as one of the most, if not the most, effective livestock agencies in the country. Its

efficiency and progress have been largely due not only to its splendid personnel over the years but also to the manner in which it was established by the legislature, making it possible to function independently and, unlike most state departments, free from political interference or other outside pressures. Because of this recognition as an agency having a wide and important influence on the rural economy of the state, there have been repeated efforts to amend the law under which it was established—either to change the manner in which it is constituted to make the board and its executive officer more amenable to political influence or, more recently, to abolish the board, placing the control of livestock disease and its other functions under some politically operated department of state.

Dr. West has taken an active part in resisting all such moves. Thus, the board has been allowed to continue to serve the public without fear of favor or regard to political expediency. No problem has been too small for Dr. West to consider nor too large for him to tackle. When he became secretary and executive officer of the board, the national campaign to eradicate bovine tuberculosis had reached the point where, in 1940, all counties in the United States had been declared Modified Accredited Tuberculosis Free Areas. A nationwide period of complacency toward bovine tuberculosis had set in. Only by the utmost persistence were the few livestock sanitarians who recognized the continuing jeopardy to the eradication program, the livestock economy, and the public health while centers of infection still remained able to obtain funds and personnel to continue a systematic tuberculin testing program, with the object in view of complete eradication of this disease from the United States. As a member of the committee on tuberculosis of the United States Livestock Sanitary Association, Dr. West worked incessantly to keep interest alive, and to revive it where it had already died, in order to continue the program that showed such promise to a final conclusion. In spite of these efforts, the tuberculosis eradication program was permitted to lag seriously in some states. Counties were reaccruited time after time after only a percentage of the herds in the area had been tested. In some states, postmortem reports from slaughtering establishments were the main criteria on which the incidence of the disease was based. The fact that, by the time demonstrable lesions have developed, great damage in the spread of this disease may have already occurred was forgotten or ignored. As a result, there has been a small but definite increase in the incidence of bovine tuberculosis on a nationwide basis in recent years.

This has not been the case in Minnesota. As a result of the Minnesota state program carried out under Dr. West's direction, the incidence of bovine tuberculosis has definitely been decreasing. The last test of all counties in the state disclosed slightly less than 0.02 per cent positive reactors among the cattle tested. In some counties that originally har-

bored heavy infection, not a single animal had a positive reaction.

The state program has required that all cattle in each county be tested at not more than six-year intervals, that every animal reported by inspectors at slaughtering places as showing lesions of tuberculosis to the herd of origin be traced, and that such herds be quarantined, subjecting all animals comprising them to the tuberculin test, properly disposing of all positively reacting animals for slaughter, and thoroughly cleaning and disinfecting the premises.

Although these results are encouraging, Dr. West points out that the job is not complete as long as even one positive reactor animal is left undiscovered in the state. Furthermore, he emphasizes the fact that, with greater movement of livestock over long distances now considered necessary to our modern agricultural economy, the job of eradication cannot be finished in one state until it has been completed on a national scale. He believes that this can and must be done, and, as soon as funds and personnel permit, the program must be extended to other species of domestic animals.

When Dr. West was appointed chief livestock sanitary official of Minnesota, the campaign to eradicate bovine brucellosis was in its infancy. He immediately accepted the challenge. Earlier research workers had demonstrated that bovine brucellosis can be readily transmitted to human beings from diseased animals. There was a high incidence of brucellosis in cattle throughout the country, including Minnesota, and human cases were appearing with increasing frequency. This was becoming a major health problem as well as being the cause of great economic loss to the livestock industry.

With the development and standardization of a simple test for brucellosis, making possible the discovery of apparently healthy carriers, a campaign was initiated to eradicate this disease from the cattle of the United States. The Minnesota State Livestock Sanitary Board, through Dr. West, was one of the leaders in the development and activation of this program, which consists largely of testing all cattle and eradicating reactors county by county and state by state, a procedure similar to that used so successfully in the eradication of bovine tuberculosis.

In connection with the simple blood test, a box container is part of the equipment; throughout the country, this is referred to as the Minnesota box and the procedure is called the Minnesota system.

As in the early days of tuberculosis eradication, much opposition developed among some cattle owners, who objected to enforced slaughter of apparently healthy animals. However, significant progress was being made, when the program was interrupted by World War II because of the resulting shortages in funds and manpower. Also, in 1941, a vaccine against brucellosis, with certain value when used in calves, was developed. Unfortunately, claims were made of the effectiveness of this product far in excess of the demonstrated facts. Many livestock own-

ers, unaware of the limitations of the immunity developed by the vaccine and influenced by the widespread propaganda broadcast by the vaccine producers, distributors, and others, felt that vaccination was the answer to the brucellosis problem. Organized opposition to the eradication program rapidly arose and was able, in many states to obtain repeal of the laws providing for compulsory participation of all cattle owners. Faced with these difficulties, the livestock sanitary authorities in many states threw up their hands, discontinued their efforts toward complete eradication, and appeared satisfied with a control program based on vaccination only.

In Minnesota, however, the vaccination problem was treated in an entirely different manner. It was determined early that, while vaccination against this disease had value as an adjunct, used alone it could only serve as a very limited control measure. The Minnesota State Livestock Board, under Dr. West's direction and almost alone among the sanitary authorities of the larger cattle-producing states, continued a complete eradication program. Results obtained by these methods in reducing the incidence of brucellosis both in cattle and in human beings were so spectacular that similar programs have now been adopted by all 50 states and the federal government. It had been made clear that, in spite of the interference with the blood agglutination test caused by vaccination, a sound program could be developed whereby vaccination could be used to its utmost capabilities without seriously interfering with an eradication program based on the blood agglutination test.

Dr. West is a man of strong determination when convinced that he is right. He never gave up for a moment his belief that sound eradication procedures should be continued. As a member of the committee on brucellosis of the United States Livestock Sanitary Association, he brought up these facts, insisting on their importance. To Dr. West must go the credit for the recognition that sound eradication procedures must be continued and reinstated where they had been dropped by the nationwide reactivation program which followed.

The tremendous efforts of the workers in the state brought the reward on June 1, 1957, of Minnesota's being declared a Modified Certified Brucellosis Area. Although this culminated long years of strenuous labor, Dr. West continued his insistence that every possible precaution be taken to prevent the spirit of complacency that followed the accreditation against tuberculosis and threatened to wreck the eradication program. With this in mind, he was instrumental in having the word "free" deleted from the title of those areas that have attained modified certified status.

Before retirement, Dr. West set up a program for orderly, systematic testing for both tuberculosis and brucellosis, whereby both programs may be carried on simultaneously, thereby saving expense as well as helping to insure against neglect or discontinuance of either program.

BATTLE AGAINST VESICULAR EXANTHEMA

This doctor, who has been so dedicated a worker throughout his years of service, can take still another bow for an additional success—preventing the entry into Minnesota of the disease of swine known as vesicular exanthema. Within a few months in 1952, this disease invaded 34 states, including all of the major hog-raising states adjacent to Minnesota, threatening the existence of the great swine industry throughout the nation. The danger was so great that one neighboring state called a special session of the state legislature to deal with the problem.

When the disease appeared in the Midwest, Dr. West promptly declared and enforced an embargo against the importation of swine from other states. He also issued orders prohibiting the assembling of swine at public sales or exhibitions. Through his quarantine authority, he prohibited the movement of any swine from the public stockyards to other points of Minnesota. Violent opposition to these measures developed, particularly by some interests at the public stockyards, but Dr. West and his staff let no attempt keep them from enforcing the measures to the letter. As a result of their combined efforts, Minnesota was the only major swine-raising state that remained completely free from this disease, saving the swine industry and the taxpayers of the state tremendous expense.

This sketch must not close without a brief expression of personal appreciation of Dr. West and his work. From the day he entered the practice of veterinary medicine at Waseca in 1919 until he became executive secretary of the Minnesota Livestock Sanitary Board on February 15, 1942, he was unknowingly preparing himself for the high positions of influence he was destined to hold in disease prevention. He conducted much of the work that was required to qualify Waseca County as a modified accredited tuberculosis-free area on July 1, 1930.

Nothing in life can be even remotely compared with practical experience. This Dr. West had in abundance when he took over the executive office of the State Livestock Sanitary Board. Indeed, it was his excellent practical work in Waseca which attracted so much attention that, in February 1941, he was appointed field veterinarian by the State Livestock Sanitary Board. In his annual report of 1942, he said, "The incidence of this disease is now negligible insofar as the loss to the livestock owners is concerned and the transmission of the disease from cattle to the human population has practically ceased." Again he said, "We do however find occasional herds in which the disease has reappeared in virulent form. If these diseased cattle were allowed to remain on the owner's premises or, still worse, the herds containing such cattle were disposed of at public auction and disseminated throughout the territory, the disease would doubtless regain a foothold and the results obtained by years of endeavor and heavy expenditure of public funds would be largely lost. It is therefore necessary that tuberculosis control be continued."

While all 87 counties in Minnesota had been designated modified tuberculosis free areas when Dr. West became executive officer, eradication of tubercle bacilli had not been accomplished, since accreditation only meant that the percentage of reactors had been reduced to at least 0.5 of 1 per cent. Thus, in the aggregate, there were still many infected animals and the program of eradication needed to be continued. It was as important to hold the line and keep decreasing the percentage of tuberculin reactors as it was to do the original work leading to the modified accredited tuberculosis-free rating. This Dr. West has done in an admirable way since 1942—so well, in fact, that for several years before his retirement only 1 in 5,000 animals tested reacted to tuberculin. He knew the potentialities of the single reactor in 5,000 and therefore continued periodic testing of the 4,000,000 cattle in Minnesota. How fortunate that Dr. West was at the helm. If this work had not been done, in all probability tuberculosis among animals would have resumed a high position during the past eighteen years. If this program is not continued, tuberculosis among animals is likely to regain its former position within the next quarter of a century.

From 1903 to 1958, the tuberculin test was administered 28,521,850 times to the cattle of this state. During this period, 258,606 animals were slaughtered and examined postmortem because they reacted to tuberculin. Dr. West's contention is that this investment must not be lost and that the information that has been gained on the way to this phenomenal accomplishment must be used.

In addition to the tremendous economic accomplishment, an even more important public health achievement was gained. When the Gillette State Hospital for Crippled Children was founded in St. Paul in 1897, and for some years thereafter, 50 per cent or more of the patients were admitted because of tuberculosis in bones and joints. Now, for more than a year, no case of bone or joint tuberculosis has been admitted to that institution. Dr. C. C. Chatterton, long-time medical director of the Gillette Hospital, has stated that the decrease in admission of bone and joint tuberculosis became noticeable after pasteurization of milk was extensively employed but more so as the eradication program among the cattle herds proceeded and after the disease was better controlled among people. There is good reason to believe that the campaign against the bovine type of tubercle bacillus reduced acute fatal forms of tuberculosis, including meningitis, in people by 25 per cent, lesions of the skin and lymph nodes by 50 per cent, lesions of the skeletal system and genitourinary tract by 20 per cent, and pulmonary disease by 1 per cent or more.

Ralph West is one of America's truly great citizens of all time. His tremendous amount of information and his practical application of it; his trustworthiness in every respect; his sincerity and honesty; his superb accomplishments; and that all-important attribute, *common sense*, have caused him to be chosen

for numerous important posts having to do with the betterment of his country as well as the positions of leadership he has held in Minnesota for so long with such significant achievements.

I have seen Dr. West preside over large national bodies, over important national committees, and over his own State Livestock Sanitary Board. I have heard him give advice before medical and public health groups from a fund of knowledge on the subject under discussion which far surpassed that of anyone else present.

Because of Dr. West's steadfast characteristic of maintaining his principles in the eradication program, he became a great defender. He was often in the center of controversy after controversy on both state and national levels. Throughout his years as

the chief livestock sanitary officer, Dr. West has had the same goals before him: the eradication of disease among domestic animals, the welfare of the livestock industry, and the health of the public. He has resisted any effort that might modify his control procedures for the sake of expediency. Under the leadership of this great general in the fight against disease, Minnesota remains today one of the safest places in the world to produce livestock. The boy who wanted to become a farmer became one of the greatest benefactors of every farmer in this and many other states. His motto has always been, like that of his predecessors in office, "There can be no compromise with disease."

The author wishes to thank Miss Dorothy Riley for her assistance in the preparation of this manuscript.

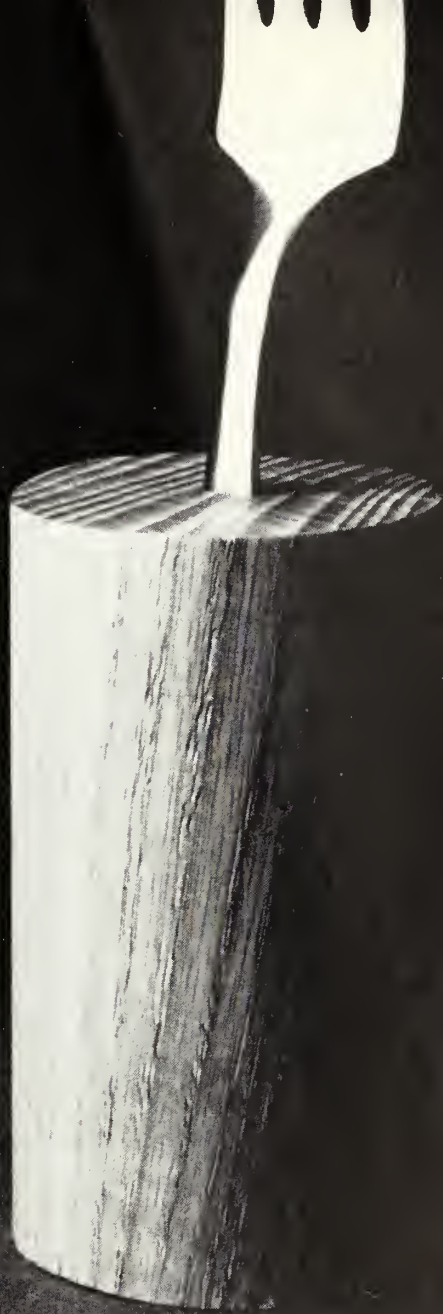
DETERMINATION of the plasma concentration of prothrombin is essential for accurate control of anticoagulant therapy. The one-stage prothrombin time of Quick may lead to false conclusions concerning efficacy of coumarin anticoagulants, since initial values actually reflect a fall in the concentration of factor VII, proconvertin, rather than a decrease in the concentration of prothrombin. Since factor VII is apparently a hemostatic agent, not essential to intravascular clotting, rapid-acting anticoagulants such as heparin should be administered until prothrombin concentrations are reduced to therapeutic levels, usually for five to seven days.

Excessive prolongation of the Quick time is not usually associated with hemorrhage during the early phases of treatment, unless prothrombin concentration concomitantly falls below 10 per cent. Prothrombin levels less than 10 per cent of normal may induce hemorrhages, most commonly from the urinary tract, less frequently from the gastrointestinal tract or skin. An obscure lesion should be suspected when bleeding is noted in patients with prothrombin concentrations greater than 10 per cent of normal.

After ten days of treatment, only periodic verification of the Quick time by the more difficult and time-consuming prothrombin concentration test is necessary, since results are frequently similar.

Prothrombin time and prothrombin concentration were determined in 280 patients during weekly to monthly visits over a period of a year and a half. In those whose prothrombin time was from two to two and a half times the control value, prothrombin concentration was less than 10 per cent of normal in over 21 per cent. In those whose prothrombin time was less than twice the control values, prothrombin concentration was 10 to 24 per cent of normal in 63 per cent. Apparently, in many, smaller doses of anticoagulants would have been effective and risk of hemorrhage thereby reduced. Probably, the usually accepted limits for prothrombin time should be reconsidered for patients given long-term therapy.

J. C. OWENS, ET AL.: Determination of prothrombin concentration as an index of anticoagulant control. *Am. J. Cardiol.* 8:471-480, 1961.



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Book Reviews . . .

Differentiation Between Normal and Abnormal in Electrocardiography

ERNST SIMONSON, M.D., 1961. St. Louis: C.V. Mosby. 328 pages. Illustrated. \$13.50.

The question has often arisen in the clinical practice of physicians: "What is a normal electrocardiogram?" Dr. Simonson and associates have put a great deal of information together on a subject of universal medical importance. The nonscientist should appreciate the author's intensive compilation of tabular data and statistical evaluation, particularly as it concerns normal range limits and distribution of electrocardiographic patterns. This book could also be read by the practitioner wishing to learn something of the basic problems with which electrocardiographers are faced. It is of great value to the internist, especially if he is engaged in teaching the fundamentals of electrocardiography.

A critique of present electrocardiographic standards depicts the problems in selecting a sample representative of an average healthy population. Degrees of electrocardiographic normality do not seem to correlate with degrees of clinical health. Within the range of "normal records" are included great variations. This fact is clearly pointed out by the author. The importance of this technical or biologic variability merely shows that the electrocardiogram as a "predictor" of future cardiac disease is a weak prognostic tool, in most instances.

An analysis of the electrocardiographic effects of tolerance to stress was most interesting and informative. The many different patterns that develop during and after exercise, meals, hypoxemia, drugs, hyperventilation, change in body position, and so forth, have been adequately described.

An admirable luxury in such a comprehensive book is an imposing list of 472 references for further information on detail.

The primary aim for writing this book has been accomplished; the pitfalls of calling an electrocardiogram "normal" are elucidated. This inspiring work is recommended for both the medical student and the physician.

THOMAS C. PUCHNER, M.D.
Milwaukee, Wisconsin

Nursing Home Administration: Training Materials for Administrators of Nursing, Boarding, and Mental Hygiene Homes for the Aged

JOHN D. GERLETTI, C. C. CRAWFORD, and DONOVAN J. PERKINS, 1961. Downey, Calif.: Attending Staff Association. 472 pages. \$6.50.

The volume is timely and important. It is timely because in the last decade we have witnessed both a planned and a mushroom growth of nursing homes. Their establishment under nonprofit, governmental, and voluntary, as well as proprietary, auspices was motivated not only by proved social needs but also by commercial opportunism. This diverse character of sponsorship, motivation, and objective generated an avalanche of scattered and isolated reading material, facts, and opinions concerning the character of the nursing home clientele and the various

modes of their optimum accommodation. Those in the field who wanted to learn had to do it in a sporadic and unsystematic method.

This book is important because (1) it is the result of a comprehensive, broadly based, and competently supervised research project with immediate and long range educational objectives for which additional studies are planned; (2) it undertakes an inventory and synthesis of current practices and points out the gaps in knowledge; (3) it contributes substantially toward a definition and content of a discipline which should require theoretical and practical training along a carefully established curriculum; and (4) it promotes the upgrading and eventual accreditation of the profession of nursing home administration by suggesting the inclusion of its essential subject matters in the teaching programs of colleges and universities.

It will be useful to medical and social work practitioners to acquire better knowledge of this growing service resource and to evaluate the actual performance of such a home in relation to advertised promises and projections. Above all, it will lead present and future administrators toward a broader understanding of the complexity and implications of the nursing home "industry" and their social responsibility within it.

Of the 11 manuals within the volume, the first 3 describe the basic principles and objectives of patient care, relationship to families, and relationship to outside trades and professions which serve the nursing home. The other 8 revolve around technical aspects of management, such as plant and housekeeping, recording, finances, meals, personnel, executive leadership, and public relations. In all of them, sound principles are developed and stated in simple language. They are based on hundreds of "ideas" which were screened and distilled in professionally guided workshops on each subject. It is also commendable that, in each chapter, the reader is advised of the necessity for continuous study.

Since a second edition is planned, we welcome the promise of better typesetting and suggest a cross index of bibliography according to author, titles, and subjects, corresponding to the 11 chapters. The practical application of the suggestions in this book would be advanced if it were supplemented by a series of work books with sample forms, charts, questions, spot checks, and step-by-step descriptions of things to do and how to do them, in each subspecialty. Such a volume was recently published by the American Nursing Home Association on as specific and related a topic as "How to be a Nursing Aid in a Nursing Home."

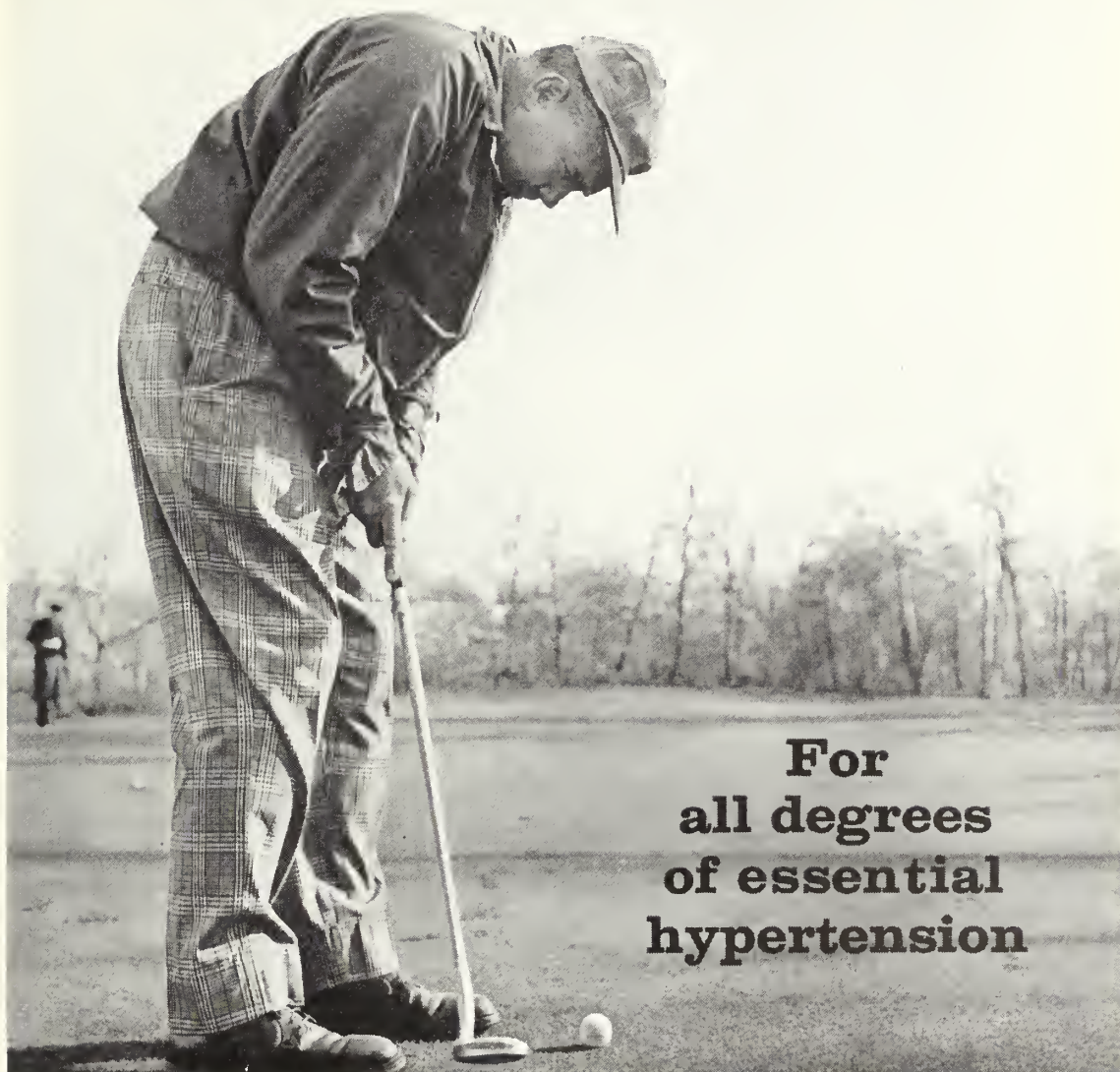
SOLOMON GELD, PH.D.
Clifton, New Jersey

Anesthesiology Symposium: Postanesthetic Complications

JAMES E. ECKENHOFF, M.D., editor, 1961. Philadelphia: J. B. Lippincott. 216 pages. Illustrated. \$2.00.

This volume of *Anesthesiology* contains the symposium, Postanesthetic Complications. The articles included are as follows:

(Continued on page 14A)



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[†]Hutchison J. C.: *Current Therap. Res.* 2:487 (Oct.) 1960.

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BOOK REVIEWS

(Continued from page 12A)

"The Failure to Regain Consciousness after General Anesthesia," by Frederick P. Hangen, M.D. This article, which is an effort to explain one of the special problems in general anesthesia, is backed by 67 references.

"The Incidence and Etiology of Postanesthetic Excitement: A Clinical Survey," by James E. Eckenhoff, M.D., Dorothy H. Kneale, R.N., and Robert D. Dripps, M.D. The valuable aspect of this paper is an examination of the 5.3 per cent of 14,436 patients given anesthetics who showed emergence excitement and the reasons why they had such a reaction. Included are 11 references.

"Postanesthetic (Postoperative) Emotional Responses," by Nathan Schnaper, M.D. This article is a discussion of the emotions and is an exercise in psychology. To follow the thinking of an experienced individual in this field is probably better than to wander through it unguided. It includes 27 references and a bibliography of 9.

"Neurological Sequelae of Spinal Anesthesia," by Nicholas M. Greene, M.D. This discussion of a delicate subject necessarily includes medicolegal considerations. It points out that not only nature but lawyers have succeeded in making it difficult to provide the patient with the anesthetic that gives the best possible opportunity of success at the time and place where the operation is to be done. There is a good bibliography of 91 references.

"Inadequate Postanesthetic Ventilation," by Willy H. Dam, M.D., and Niels Guldman, M.D. This timely article calls attention to the hazard of respiratory depression that is seen all too often with the techniques used in modern anesthesia. A bibliography of 72 references is included.

"Atelectasis, Pneumothorax, and Aspiration as Postoperative Complications," by William K. Hamilton, M.D. This aspect of anesthesia practice needs to be reviewed frequently and is well reviewed here. A bibliography of 92 references is included.

"Postoperative Cardiac Arrhythmias," by Joseph J. Buckley, M.D., and J. Albert Jackson, M.D. This is a subject of special interest and deserves to be treated in this symposium as one of the important studies which should be carried out in the postoperative period. There are 59 references included.

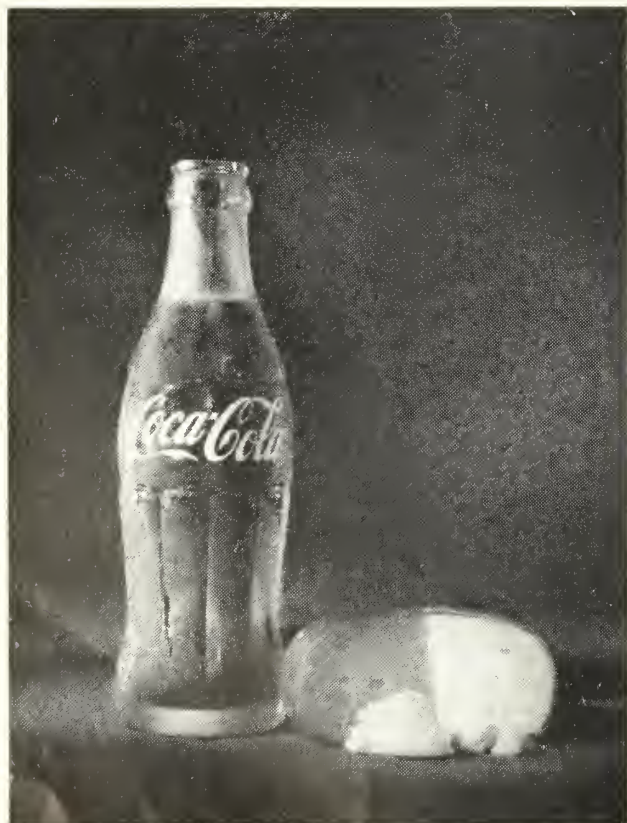
"Sudden Cardiac Collapse: Cardiac Arrest and its Treatment," by Stevens J. Martin, M.D. This tantalizing subject is given thoughtful treatment by an author whose ideas are always provocative. Included is a bibliography of 117 references.

"Embolie Phenomena of the Operative and Postoperative Period," by Robert T. Patrick, M.D., and Robert A. Devloo, M.D. This timely article needs to be read by more individuals than those it will probably reach. There are certain medicolegal situations which might pass unexplained if this article were not read. It is supported by a bibliography of 46 references.

"Failure of the Peripheral Vascular Circulation," by Kenneth Sugioka, M.D., and Doris C. Grosskreutz, M.D. This is a discussion of a phenomenon seen in the postoperative period. It is well worth reviewing as the authors have given a fine bibliography of 188 references. This is an important part of the symposium.

"Postanesthetic Nausea and Vomiting," by J. Weldon Bellville, M.D. This condition has caused concern ever since the introduction of ether; the treatment for it is always debatable. The bibliography includes 30 references.

(Continued on page 16A)



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Vaginal Approach to Pelvic Surgery, One Week, May 14
Obstetrics, General and Surgical, Two Weeks, April 30
Pain Relief in Childbirth, 3 Days, July 11
Proctoscopy and Sigmoidoscopy, One Week, July 16
General Practice Review, One Week, May 21
Advanced Electrocardiography, One Week, June 18
Gallbladder Surgery, 3 Days, June 18
Surgery of Hernia, 3 Days, June 21
Neuromuscular Diseases, Two Weeks, June 11
Hematology, One Week, June 4
Advances in Medicine, One Week, May 7
Blood Vessel Surgery, One Week, May 14
Breast and Thyroid Surgery, One Week, May 21
Fractures and Traumatic Surgery, Two Weeks, June 11
Diagnostic Radiology, Two Weeks, April 23

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BOOK REVIEWS

(Continued from page 14A)

"Renal Complications After Anesthesia and Operation," by Antonio Boba, M.D., and Charles M. Landmesser, M.D. Postoperative oliguria and anuria are included in this discussion, which has a bibliography of 33 references. Few factors are more important than the mechanism of water and electrolyte balance.

"Postoperative Temperature Changes," by C. R. Stephen, M.D. This provocative subject is briefly and carefully handled. Actually not too much factual knowledge is available. There are 14 references.

"Complications Related to Body Positions During Surgical Procedures," by John R. Lincoln, M.D., and Howard P. Sawyer, Jr., M.D. It is high time that somebody dealt with the subject of posture during anesthesia. The inclusion of 87 references emphasizes the general feeling that this should be stressed.

"Untoward Reactions and Complications During Transfusions and Infusions," by Thomas H. Seldon, M.D. The author of this article is thoroughly grounded in the subject he discusses and, for that reason, is able to say much in a few words. Twenty references are included.

"Postoperative Changes in Electrolyte Balance," by James D. McMurrey, M.D., and Sam W. Law, M.D. This intriguing subject is illustrated with graphs which make the contents of this article very significant. For those who hope to achieve the best surgical results, this subject must be constantly kept in mind. There are 34 references.

A copy of the entire symposium may be obtained from the Circulation Department of *Anesthesiology*, J. B. Lippincott Company, East Washington Square, Philadelphia 5, Pennsylvania. The collected reprints should be ordered while the supply lasts. Reprints of individual articles are not available.

JOHN S. LUNDY, M.D.
Chicago

New Books Received

Books and publications received will be listed here periodically, and such mention must be regarded as sufficient return for the courtesy of the sender. Books of special interest to our readers will be reviewed as space permits.

The Art of Thinking. DAGOBERT D. RUNES, 1961. New York: Philosophical Library. 90 pages. \$2.75.

Baillière's Nurses' Dictionary. Revised by BARBARA F. CAPE, 15th edition, 1961. Baltimore: Williams & Wilkins. 540 pages. Illustrated. \$2.25.

Basic Biochemistry. M. W. NEIL, 1961. Philadelphia: J. B. Lippincott. 360 pages. Illustrated. \$6.75.

Biological Activity of the Leucocyte. G. E. W. WOLSTENHOLME and MAEVE O'CONNOR, editors, 1961. Boston: Little, Brown & Co. 120 pages. Illustrated.

Dictionary of Aphrodisiacs. HARRY E. WEDECK, 1961. New York: Philosophical Library. 256 pages. Illustrated. \$10.00.

Essentials of Neurology. JOHN N. WALTON, 1961. Philadelphia: J. B. Lippincott. 422 pages. Illustrated. \$6.75.

The Ford Foundation Annual Report—1961. New York: The Ford Foundation. 176 pages.

BOOK REVIEWS

Halothane (Fluothane). C. RONALD STEPHEN and DAVID M. LITTLE, JR., 1961. Baltimore: Williams & Wilkins. 142 pages. \$6.00.

Health Organizations of the United States and Canada. CLARA S. WASSERMAN, 1961. Ithaca, N. Y.: Cornell University Press. 191 pages. \$10.00.

Histopathology of the Skin. WALTER F. LEVER, 3rd editions, 1961. Philadelphia: J. B. Lippincott. 653 pages. Illustrated. \$16.50.

A Mirror Up To Medicine. A. C. CORCORAN, editor, 1961. Philadelphia: J. B. Lippincott. 506 pages. \$5.75

Nature of Sleep. G. E. W. WOLSTENHOLME and MAEVE O'CONNOR, editors, 1961. Boston: Little, Brown & Co. 416 pages. Illustrated. \$10.00.

Optics: An Introduction for Ophthalmologists. KENNETH N. OGLE, 1961. Springfield, Ill.: Charles C Thomas. 257 pages. Illustrated. \$8.75.

The Origin of Medical Terms. HENRY A. SKINNER, 2nd edition, 1961. Baltimore: Williams & Wilkins. 437 pages. Illustrated. \$12.50.

Poliomyelitis. INTERNATIONAL POLIOMYELITIS CONGRESS, editors, 1961. Philadelphia: J. B. Lippincott. 435 pages. Illustrated. \$7.50.

Problems of Pulmonary Circulation. A. V. S. DE REUCK and MAEVE O'CONNOR, editors, 1961. Boston: Little, Brown & Co. 96 pages. Illustrated. \$2.50.

Progesterone and the Defense Mechanisms of Pregnancy. G. E. W. WOLSTENHOLME and MARGARET P. CAMERON, 1961. Boston: Little, Brown & Co. 108 pages. Illustrated.

Somatic Stability in the Newly Born. G. E. W. WOLSTENHOLME and MAEVE O'CONNOR, editors, 1961. Boston: Little, Brown & Co. 393 pages. Illustrated. \$10.00.

W. K. Kellogg Foundation Annual Report—1961. Battle Creek, Mich.: W. K. Kellogg Foundation. 170 pages.

Essential Hypertension: An International Symposium. K. D. BOCK and P. T. COTTIER, editors, 1960. Boston: Little, Brown & Co. 392 pages. Illustrated.

The List Method of Psychotherapy. E. SHER, E. MESSING, T. HIRSCHHORN, E. POST, A. DAVIS, and A. MESSING, 1960. New York: Philosophical Library, 252 pages. \$7.50.

Management of Pediatric Practice: Philosophy and Guide. HUGH C. THOMPSON, M.D., and JOSEPH B. SEAGLE, M.D., 1961. Springfield, Ill.: Charles C Thomas. 160 pages. Illustrated. \$7.50.

Manual of Clinical Bacteriology. ALEXANDER KIMLER, 1961. Philadelphia: J. B. Lippincott. 201 pages. Illustrated.



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News Briefs . . .

General

THE CHICAGO OPHTHALMOLOGICAL SOCIETY will sponsor a 6-month basic pre-residency course in ophthalmology, beginning July 9, 1962. The course is intended for graduates of accredited medical schools who seek residencies or preceptorships in ophthalmology. The course will be presented at the Cook County Graduate School of Medicine, 707 South Wood Street, Chicago 12, Illinois. Detailed information will be provided upon request.

CARE AND MEDICO have merged to reduce the costs of relief work in foreign countries. MEDICO, founded in 1958 by the late Dr. Tom Dooley and Dr. Peter D. Comanduras, will serve as a professional arm of CARE and will continue to send teams of medical specialists overseas, using medical supplies and equipment provided by CARE. Before the merger, MEDICO had 20 medical teams and programs in 12 countries. CARE operates in 32 countries, supplying food, kits of farm implements, and other necessities.

THE PUBLIC HEALTH SERVICE, through the Venereal Disease Program, is providing literature to counter the alarming rise of infectious syphilis since 1957. Abstracts of articles on venereal disease from nearly 1,000 foreign and domestic journals are printed in "Current Literature on Venereal Disease," published several times each year and indexed annually. The publication is distributed free of charge to physicians who send requests to William J. Brown, M.D., Chief, Venereal Disease Branch, Communicable Disease Center, Atlanta 22, Georgia.

North Dakota

DR. BRIAN E. BRIGGS, who has been on the medical staff at the Great Plains Clinic in Minot since 1959, has moved to California, where he is now associated with the Cordova Medical Group at Rancho Cordova, a suburb of Sacramento. Dr. Briggs received his medical degree from the University of Minnesota Medical School and interned at St. Mary's Hospital in Duluth.

DR. ALBERT H. FORTMAN, JR., has joined the staff of the Capital City Clinic in Bismarck. Dr. Fortman, a native of Shelby, Montana, received his medical degree at the Northwestern University Medical School and did post-graduate work at Cook County Hospital in Chicago in general and thoracic surgery. He was associated most recently with the Northwestern Clinic at Crookston, Minnesota.

DR. OTTO C. GAEBE, honored by New Salem in 1950 for his forty years of service to the community, was recently given a testimonial banquet by the New Salem Lions Club. Dr. Gaebe was presented with a plaque by the club to mark his work in New Salem and his activities as a charter member of the organization. Dr. Gaebe

received his medical degree from the University of Southern California Medical School.

DR. PAUL W. FREISE has been re-elected president of the Bismarck Hospital medical staff. Also re-elected to staff positions were Drs. Norvel O. Brink, vice-president; Robert B. Tudor, secretary; and Phillip Dahl and C. H. Peters, members at large.

DR. C. M. HUNTER of Fargo has succeeded Dr. Howard G. Hall as president of the First District Medical Society. Dr. Frank M. Melton and Dr. Richard J. Zauner, also of Fargo, were elected vice-president and secretary-treasurer of the society.

DR. JOSEPH LALTOO, formerly on the staff at the Dakota Clinic of Fargo, has opened a private practice in Ashley. Dr. Laltoo will also serve the local hospital and will replace Dr. Karl Oja, who has discontinued his practice in Ashley.

DR. RALPH E. LEIGH has been elected chief-of-staff and president of the executive board at St. Michael's Hospital in Grand Forks, succeeding Dr. Nelson A. Youngs. Dr. Leigh has been a member of the medical staff at St. Michael's for thirty-six years. He is president of the North Dakota Chapter of the American College of Surgeons and head of the Department of Obstetrics at the University of North Dakota Medical School. Other officers of the executive board are Drs. Frank A. Hill, vice-president, and Kenneth S. Helenbolt, secretary. Members of the board include Drs. Walter C. Dailey, John McLeod, and Dr. Leonard J. Prochaska, who have replaced Drs. Louis B. Silverman and James D. Cardy.

DR. ROBERT B. NOLAN, a specialist in pediatrics, has become a member of the staff of the Children's Clinic in Jamestown, joining Dr. James V. Miles. A native of Omaha, Nebraska, Dr. Nolan received his medical degree at the Creighton University School of Medicine, Omaha. He specialized in child care in the fellowship training program at the Mayo Clinic in Rochester, Minnesota.

Minnesota

THE MAYO CLINIC board of governors has re-elected officers for 1962 with Dr. J. T. Priestley as chairman for a sixth term. Dr. C. A. Good is vice-chairman, and J. W. Harwick, secretary. Named to the personnel committee were Dr. J. M. Stickney, chairman; Drs. Priestley, O. H. Beahrs, J. W. DuShane, L. E. Ward, G. S. Schuster, and Mr. Harwick as secretaries; Dr. Victor Johnson, ex officio member; and Dr. R. D. Miller as an alternate.

Administrative committee members are Dr. Priestley, chairman; Dr. DuShane, vice-chairman; Drs. C. W. Mayo, Good, Stickney, Ward, Mr. Schuster, and Mr.

(Continued on page 20A)

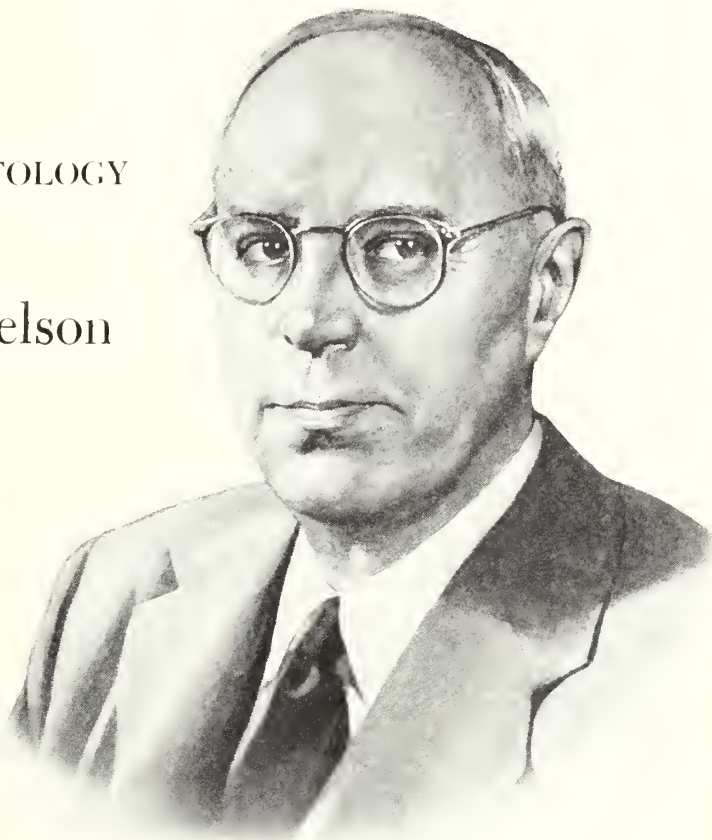
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Honoring

Dr. Henry E. Michelson



DR. HENRY MICHELSON was my first teacher of dermatology, and for more than thirty years I have admired him both as a man and as an outstanding leader in his specialty. The brilliant clarity and general excellence of his lectures to undergraduate students were impressive and, in fact, prompted my decision to enter the specialty of dermatology. At the time that I attended medical school, lectures in dermatology were given during the junior year. They were so stimulating that I attended them during my senior year, during three years of a fellowship in dermatology, and for twenty-five years thereafter, whenever the opportunity presented itself. Even though the same cutaneous disorder had been discussed many times before, there was always an opportunity to increase one's knowledge of the subject.

During my early years in practice, Dr. Michelson, along with Drs. Francis Lynch, Louis Winer, Elmer Rusten, the late John Madden, and me, attended many meetings of the Chicago Dermatological Society, where he introduced all of us neophyte dermatologists to the men in that group, enabling us to form many enduring friendships. Later, we attended many other dermatologic meetings from New York to the West Coast and from Canada to the Gulf. He constantly paved the way for the younger men, enabling them to widen their dermatologic horizons and to make new friends in their field.

Dr. Michelson, even though engaged in a busy private practice and serving as director of the Division of Dermatology at the University of Minnesota, could always find time to give sound advice, dermatologic or otherwise, concerning problems which confronted younger colleagues. It is difficult to express one's deep appreciation for these many kindnesses.

All of the men who have contributed to this issue of THE JOURNAL-LANCET were students of Dr. Michelson. All of us feel honored to show a slight token of our appreciation for the many fine things which he has done for us.

CARL W. LAYMON, M.D.
Guest Editor

EDITOR'S NOTE: *A profile of Dr. Henry Michelson may be found in the July 1961 issue of THE JOURNAL-LANCET, pages 304-308.*

Some Unusual Problems in Cutaneous Malignancy

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THE 10 CASE HISTORIES which follow are presented as examples of unusual problems in cutaneous malignancy with the hope that such a report may aid physicians in the future when they encounter similar odd cases.

CYLINDROMA OF THE PAROTID GLAND

Case 1. In March 1952, a 38-year-old woman was examined because of severe neurotic excoriations of ten years' duration on her face. Examination showed, in addition to the excoriations, a firm nodule 2 cm. in diameter behind the right ear which had been present for five years. About six months after the tumor's onset, she had consulted a dermatologist in another city, who possibly could have saved her life had he made a correct diagnosis. He assured her that it was a cyst and pointed to a lesion behind his own ear, which, he stated, was identical. After examination in 1952, she was referred to a surgeon and the lesion was excised. Histologic diagnosis was cylindroma of the parotid gland. The patient remained well until August 1953, when the tumor recurred in the same location. In September 1953, the lesion was excised again. At the time of last examination, in February 1954, there was no evidence of the tumor. The patient died in 1957 because of pulmonary metastases.

Discussion. The term cylindroma, as used by dermatologists, indicates a disease characterized by multiple tumors of variable size situated on the scalp, although frequently there is only a solitary lesion that may be either on the scalp or on the glabrous skin. The histopathologic picture is usually diagnostic. There are basal cells in round, oval, or elongated masses, appearing usually in solid globules and surrounded by a hyaline-like connective tissue membrane (figure 1). Hyaline changes are to be seen between the tumor cells and intracellularly. The outer row of cells next to the hyalinized connective tissue membrane usually has a palisade arrange-

ment. The cells in the center may show early signs of hyaline degeneration and formation of cysts. Sometimes, the tumor cells grow in narrow strands in an alveolar-like arrangement and are strongly suggestive of aberrant sweat glands. Histologic findings may suggest erroneous diagnoses of adenoma or carcinoma of the sweat glands. Several unsuccessful attempts have been made to trace connection with either sweat glands or sweat ducts. Apparent origin from the basal cells of the epidermis and from the basal cells of the outer surface of the walls of the hair follicles, however, has been repeatedly demonstrated. The disorder is considered benign and nevoid.

In this case, the tumor was a cylindroma of the parotid gland which had a vastly different outlook. Dockerty and Mayo¹ point out that there occasionally arises in the submaxillary glands a type of neoplasm known as cylindroma, adenocarcinoma (cylindroma type), or basal-cell carcinoma with hyaline stroma. The incidence of this tumor is approximately 20 per cent. The tumor has been confused with the ordinary type of mixed tumor. In this type of cylindroma, recurrence is extremely high and metastases are frequent. More than 50 per cent of patients die from the effects of widespread dissemination of the disease. Clinically, cylindromas cannot be distinguished from the group of mixed tumors,

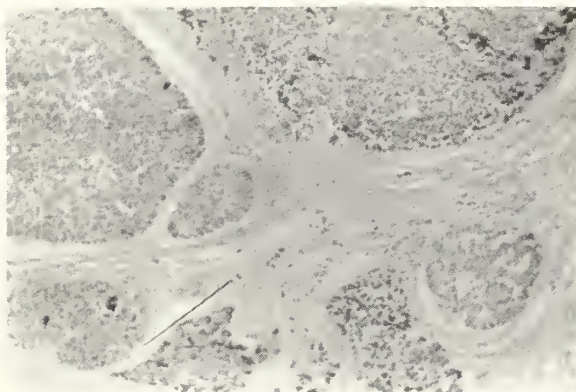


Fig. 1. Case 1. Cylindroma of parotid gland. Oval masses of darkly staining cells surrounded by connective tissue membrane

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although pain is a contrastingly frequent symptom. Surgically, the infiltrative tendencies observed by the surgeon make him sometimes question a fresh tissue diagnosis of mixed tumor. In the Mayo communication, distinctive microscopic features of cylindroma were presented, and it was shown that the surgical pathologist familiar with the cellular pattern could render a real service in advising radical operative procedures when such a neoplasm was encountered.

For a long time, investigators confused mixed tumors with cylindromas. Quattlebaum and associates² considered a series of primary neoplasms of the parotid gland to ascertain whether or not cylindromas occurred there and, if so, whether or not their clinical behavior was that of their submaxillary counterparts. They reviewed 210 consecutive cases in which primary parotid tumors had been removed surgically at the Mayo Clinic between the years 1928 and 1936, inclusive. These were carefully studied microscopically, and 21 tumors (10 per cent of all parotid tumors), many of which had been previously labeled mixed tumors, fulfilled the criteria for a diagnosis of cylindroma.

Histologically, the general architecture of these tumors was that of islands and strands of small, dark-staining cells with hyperchromatic nuclei. Many of the units demonstrated central honeycombing with clear spaces, which in some instances were filled with hyaline substances and in others, with globules of material which stained positively for mucus. Infiltrative tendencies were pronounced. The tumor capsule, the attached parotid glandular substances, and the surrounding fat frequently showed invading strands of tumor tissue extending from the parent growth.

In this series, men and women were involved almost equally. The average age of the patients was 49.8, with extremes of 32 and 65 years. At the time of examination, the duration of the

swelling varied from six months to fifteen years, with an average of about seven years. It was thus impossible to judge on the basis of duration the nature of the underlying pathologic process. Eight of the 20 patients succumbed within five years to the effects of metastasis, 5 with evidence of pulmonary spread; 2 died more than five years after operation; and 4 of the remaining 10 had inoperable recurrences at the time of the report. It is obvious that early, radical, surgical procedures must be done in order to obtain better results in the treatment of cylindroma of the parotid gland, as is exemplified in the case presented here.

MALIGNANT MELANOMA OF EYELID

Case 2. This 67-year-old man was examined first in September 1949. He had a lesion on the left upper eyelid of approximately two years' duration. His chief symptom was that he was unable to open his left eye because of the weight of the growth.

Examination showed a large, black mass involving the entire upper eyelid and periorbital region on the left side (figure 2). The retina, cornea, and iris showed no abnormalities. The patient had noticed no visual disturbances. In September 1949, he refused treatment and seemed rather proud of the unusual growth on his face. On biopsy, histologic findings were those of malignant melanoma. A month later, in October 1949, the patient changed his mind and radical excision of the lesion with enucleation of the left eye was done. In June 1950, there was a local recurrence, which was excised; radon seeds were implanted. Careful physical examination showed no metastatic lesions. The patient failed to return thereafter for further examination and his final fate is unknown.

Discussion. It is generally agreed that the eye is a rather frequent primary site of malignant melanoma. These tumors arise chiefly from the choroid and less often from the ciliary body or iris. Most of the tumors develop in patients after the age of 40. An intraocular malignancy in an adult is usually melanoma. It has been said that enucleation of the eye before glaucoma gives 60 to 80 per cent of cures but the prognosis is much worse after glaucoma has developed. As in melanomas in other locations, metastasis may develop many years after removal of the eye.

AMELANOTIC MELANOMA

Case 3. The patient, a 63-year-old woman, had noticed a nodule on the left cheek, about the color of normal skin, six months before the first



Fig. 2. *Case 2.* Massive black malignant melanoma of eyelid

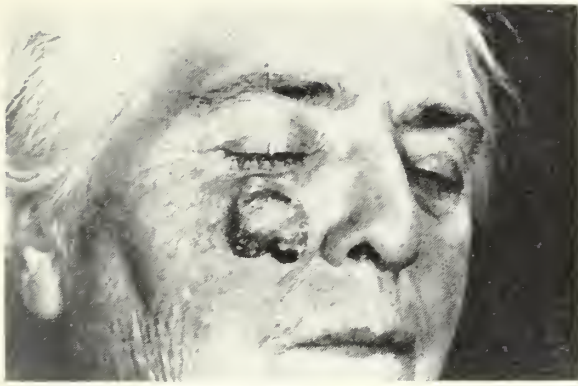


Fig. 3. Case 3. Amelanotic melanoma. When growth appeared, color was that of normal skin.

examination. It was a rapidly growing malignancy, and a general pathologist made a histologic diagnosis of atypical squamous cell epithelioma. Subsequently, 2 dermatopathologists agreed that the lesion was an amelanotic melanoma (figure 3). Despite surgical treatment, the patient died about a year later, with extensive pigmented metastases in the liver, lungs, and skin.

JUNCTION NEVUS OF THE NAIL BED

Case 4. This case is not one of cutaneous malignancy, although it is related to the previous discussion of melanoma. The 24-year-old patient was an intern at Ancker Hospital, St. Paul, Minnesota, and was first observed in 1947. In October 1943, he noticed a dark brown, longitudinal stripe at the base of the left thumb nail. This gradually progressed to the distal margin of the nail. The stripe slowly widened and, after about a year, measured 3 mm. in width (figure 4). There was no history of trauma. The patient was seen by several consultants in dermatology, surgery, and pathology. Most of them advised no radical treatment—only observation.



Fig. 4. Case 4. Junction nevus of nail bed

The intern was planning to take a fellowship in surgery; hence, removal of the thumb would be a serious handicap. He became frightened, however, and insisted that the digit be amputated. Microscopic sections through the base of the nail and the region of the matrix showed a junction nevus corresponding in extent and position to the area of the pigmented band in the nail. The patient has remained well since the operation.

AMELANOTIC METASTATIC MELANOMA SIMULATING EPITHELIOMA

Case 5. This 68-year-old man was first examined in April 1958. He stated that an eroded nodule had appeared on his right cheek near the ear a few months previously. He had consulted a



Fig. 5. Case 5. Amelanotic metastatic melanoma. Primary was never found.

physician, who told him that it was a pyogenic infection and prescribed some type of ointment. He stated also that there were 2 lumps behind his right ear which had been present for six months. Another doctor had told him not to worry about these because they were cysts and many people had them.

Examination showed a tumor, 12 mm. in diameter and superficially eroded, on the right cheek (figure 5). There were 2 firm nodules behind the right ear, each measuring 1 cm. in diameter. Epithelioma of the cheek with metastases to the regional nodes was suspected. A punch biopsy was performed and examined by a general pathologist. The entire specimen was made up of highly malignant tumor cells undergoing mitosis. There was no direct connection with the epidermis. The general pathologist

thought that the lesion was a highly malignant metastatic carcinoma (figure 6), possibly from the stomach or bowel. The patient was admitted to hospital in May 1958.

Thorough physical examination, including roentgenograms of the lungs, stomach, and bowel, showed no evidence of malignancy. Proctoscopic examination showed no abnormalities. The lesions on the right cheek and in the right mastoid region were excised widely. The tumor in the mastoid region was made up of lymph



Fig. 6. Case 5. Histologically, lesion in figure 5 simulated malignant metastatic carcinoma.

nodes and parotid glandular changes. Histologic examination showed a melanotic metastatic melanoma. Radical dissection of the right side of the neck was recommended but refused. About the middle of September, nodules appeared again behind the right ear and beneath the angle of the jaw. The patient refused further surgery; hence, x-radiation was instituted. The patient died within a year.

GUMMA AND EPITHELIOMA

Case 6. This 68-year-old patient had had multiple, deep, punched-out ulcers develop on the

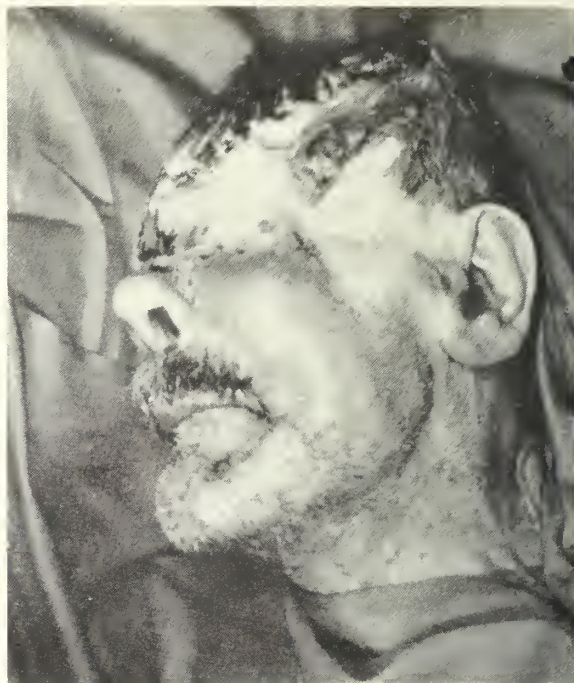


Fig. 7. Case 6. Gumma and squamous cell epithelioma

forehead and right orbital region in the summer of 1958. He was first examined a year later. He stated that he had had a sore on his penis about forty years previously, for which he had received mercury rubs. Histologic examination showed no evidence of carcinoma. Serologic tests for syphilis were positive, and treatment was instituted with injections of neoarsphenamine and bismuth. Figure 7 shows healing with scarring

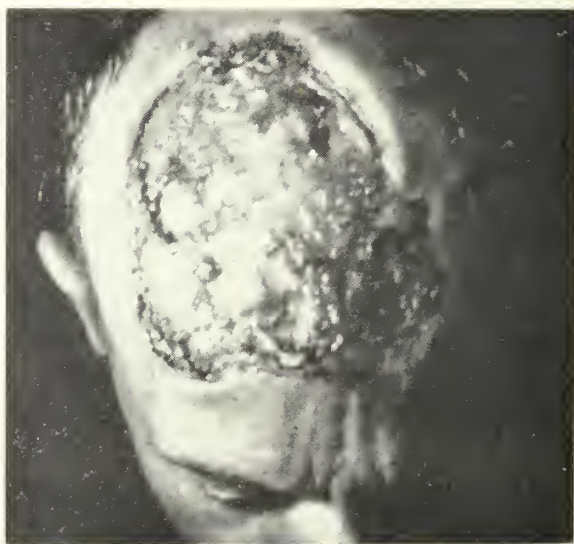


Fig. 8. Case 7. Basal cell epithelioma in patient with syphilis

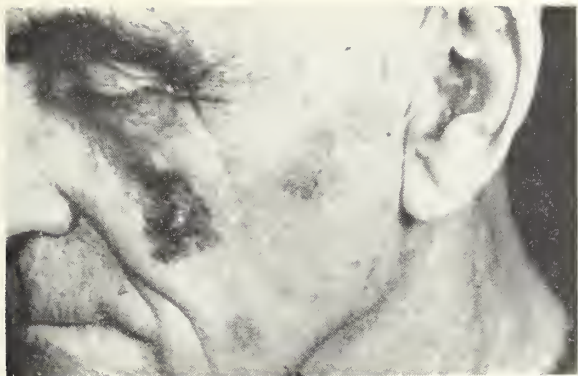


Fig. 9. Case 9. Bowen's disease. Histologically, nodule in center was squamous cell epithelioma.

three months after treatment was instituted. The upper portion of the lesion did not heal. Another biopsy was performed; squamous cell epithelioma was found and was treated by x-rays. The patient failed to return for observation, and the final outcome is unknown.

BASAL CELL EPITHELIOMA IN A SYPHILITIC PATIENT

Case 7. An ulcer had developed on the forehead of this 55-year-old man ten years before examination (Figure 8). Serologic tests for syphilis were positive, but antisypilitic treatment produced no change in the lesion. The histologic picture was that of basal cell epithelioma. The patient was treated with radium and x-rays, after which the lesion underwent considerable involution. Shortly after, pneumonia developed and the patient died.

SQUAMOUS CELL EPITHELIOMA HISTOLOGICALLY SIMULATING AMELANOTIC MELANOMA

Case 8. This 35-year-old woman was first examined in February 1958. She stated that a nodule had appeared in the right nasolabial fold seven years previously. She consulted a dermatologist, who performed a biopsy and cauterized the lesion. Histologic examination at that time showed no evidence of malignancy. Four years later, the lesion recurred, and she consulted a general surgeon, who applied some type of chemical. The lesion did not respond to this treatment, so electrocauterization was used. There was no further recurrence until six months before the present examination in February 1958, which showed an ulcerated nodule 0.5 cm. in diameter lateral to the right nostril. A general pathologist made a diagnosis of squamous cell epithelioma. The lesion was treated with x-rays during March 1958. Examination in May 1958 showed that the lesion had involuted. The patient was reexam-

ined in June, by which time the nodule had reappeared. At this time, a pathologist made a histologic diagnosis of amelanotic melanoma.

The patient's uncle was a Catholic priest, who urged her to fly immediately to Lourdes, France, to pray at the shrine. A friend in whom malignant melanoma had developed while she was pregnant went to Lourdes and prayed that her child be spared from melanoma. She gave birth to a normal infant who survived without melanoma. The mother died a short time later with metastases.

Because the histologic picture was confusing in this case, another dermatopathologist and 2 other general pathologists were consulted. All agreed that the lesion was a squamous cell epithelioma and not an amelanotic melanoma. After the pathologists agreed that the lesion was not melanoma, the patient decided not to go to France. The recurrent lesion was thoroughly cauterized in June 1958, and she has had no difficulty since.

BOWEN'S DISEASE OF THE FACE

Case 9. This 65-year-old man was examined first in April 1957. A pigmented lesion had developed on the right cheek eleven years previously. The patient had consulted a dermatologist, who stated that it was a seborrheic keratosis and cauterized it. One year later, the lesion recurred and was again cauterized. Within two years, it recurred and slowly increased in size. Since the patient had been told that it was benign and that there was nothing to worry about, he did not report again for examination until a nodule appeared in the center of the lesion. The clinical appearance suggested malignant melanoma.

Two biopsies were performed, one from the nodule and the other from the flat part of the lesion. The histologic findings from the flat part of the lesion were characteristic of Bowen's disease, while the histologic findings from the nodule indicated frank squamous cell epithelioma (figure 9). The lesion was treated with x-rays and has not recurred after eighteen months.

BOWEN'S DISEASE OF THE HAND SIMULATING CHRONIC ECZEMATOID FUNGUS INFECTION

Case 10. This 64-year-old man was examined first in August 1955. He said that his hand had been pinched in a car coupler thirty-five years before, when he was working on the Burlington Railroad. Twenty-five years later (ten years before the time of examination), a lesion developed on the left hand which extended from the dorsal surface and side of the fingers to the left palm. At the time of the examination, chronic der-

matophytosis, dermatitis repens, and Bowen's disease were among the diagnostic considerations. Cultures showed no pathogenic fungi. A biopsy was performed, and the histologic findings showed thickening of the epidermis and a mild banal inflammation in the upper part of the cutis. There was nothing which suggested Bowen's disease. Treatment consisted of fractional superficial x-rays and many different topical applications.

After several months, the results of treatment were unsatisfactory and another biopsy was performed. In this instance, there were changes characteristic of Bowen's disease. By this time, the lesion had extended to involve most of the left palm. The patient was treated by dermabrasion in April 1956. By June 1956, much of the lesion seemed to have been eradicated, although there were a few persistent erythematous scaly

areas. The patient then went on vacation for three weeks and was instructed to report for observation in one month. At that time, there were still a few areas of activity, and he was referred to a surgeon for excision. After examination by the surgeon, he failed to return for fourteen months. At that time, the lesion, which had extended, was excised and skin grafts were performed. A few recurrent nodules were subsequently observed at the border of the graft. These were excised, and there has been no further recurrence for eighteen months.

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IN WOMEN 70 years of age or older, operative mortality rate for radical mastectomy is 10 times greater than in younger women. Simple mastectomy, with or without partial axillary dissection, requires less time and anesthesia, and operative mortality is negligible. Delay in seeking treatment results in significantly larger breast tumors in the older woman. However, many are low-grade tumors and the increased axillary metastasis that usually accompanies delayed treatment is not found.

Of 242 women over 70 with breast carcinoma, 94 who were considered poor risks had modified mastectomies; 148 had radical dissections. Operative deaths occurred in 3.4 per cent of patients with radical procedures but in none of the others. Crude five-year survival rates were 39 per cent for patients with radical mastectomies and 40 per cent for those with modified operations. However, crude ten-year survival rates were 16 and 4 per cent, respectively.

J. W. BERG and G. F. ROBBINS: Modified mastectomy for older, poor risk patients. *Surg., Gynec. & Obst.* 113:631-634, 1961.

Plantar Warts in a School Population

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THE ENDEMIC and virtual epidemic incidence of plantar warts in junior and senior high school students in the Duluth schools and surrounding communities led to the following observations and control measures: (1) a period of elimination of students with known plantar warts from school pools and showers, (2) a follow-up period of no specific control measures, and (3) a comparison of the incidence of plantar warts in schools with and without pools. As a basis for judging the value of statistics in control measures for plantar warts, common knowledge about plantar warts should be reviewed.

PLANTAR WARTS

Plantar warts, and probably all types of warts—common, juvenile, mosaic, and venereal—are caused by a virus. The epidemic incidence, appearance in linear arrangement after scratch marks, occurrence on opposing surfaces (kissing warts), periungual distribution after excoriation, and tendency to spread on hyperhidrotic feet all suggest their inoculability.

In 1894, de Fine Licht¹ and, independently, Variot² inoculated warts from individual to individual. Ciuffo,³ in 1907, transferred warts with material passed through a Berkefeld filter. Basophilic nuclear inclusion bodies in epidermis from warts were described in 1924 by Lipschutz.⁴ In this country, Blank and associates⁵ confirmed this finding. In 1949, Strauss and associates⁶ demonstrated with the electron microscope the presence of virus-like particles in the supernatant fluid after ultracentrifugation of ground wart tissue. The particles varied in size from 56 to 80 μ when isolated and from 50 to 53 μ when in crystalline arrangement. Culture of wart virus particles on chorioallantoic membrane of chick embryo was reported by Bivins⁷ in 1953. Negative results of culture with a variety of techniques have been reported by Felsher⁸ and Siegel and Novy.⁹

In experimental human transfer of the virus, the incubation period was from one to eight months, except for Templeton's¹⁰ report, wherein warts appeared twelve to twenty months after inoculation. No concrete facts are known of the

existence of the virus outside actual warts, yet this possibility appears to exist when we consider plantar warts, as direct contact with other warty feet is unlikely.

Immunity to the wart virus has been suggested by spontaneous clinical remissions, resistance to reinoculation after spontaneous remission, and complement-fixation experiments. Certain observations lead to the belief that such immunity is temporary. Some reports attribute spontaneous remissions to a gradual weakening of the virus without the need for specific antibody response. I have observed that most successful treatments of warts are preceded by an inflammatory reaction about the wart. Allington,¹¹ Biberstein,¹² Conti,¹³ Samek,¹⁴ and Vollmer¹⁵ have described an inflammatory reaction in warts before spontaneous involution. This may be a Jarisch-Herxheimer, or specific antigen-antibody, reaction. Rulison¹⁶ averred that antibody formation deficiency or delay is related to development of a large number of warts in a person. Memmesheimer and Eisenlohr¹⁷ found that, in a six-month observation period, 20 of 70 control patients, or 28.5 per cent, exhibited spontaneous cure of warts. The efficacy of various and numerous methods, including psychotherapy, in curing warts has been attributed to autonomic nervous system control of capillary permeability, which affects the milieu for virus growth.

The rising incidence of plantar warts has been reported by many authors. Rasmussen,¹⁸ whose study is a classic and a great contribution to the data on plantar warts, reported 5,223 patients and showed an increased incidence in new cases of warts at the Finsen Institute from 59 in 1925 to 7,000 in 1949. This was an increase with respect to both total skin patients and the incidence of extraplanar warts, which was doubled. He concluded that probably (1) school children are exposed to the wart virus to an exceptional degree and (2) this exposure takes place while bathing in school. The higher absolute incidence of plantar warts on female feet on the great toe and forefoot, where pressure is exerted because of shoe style, was illustrated by his study. Rulison,¹⁶ Strauss and associates,¹⁹ and Osborne and Putnam²⁰ observed that the highest incidence of

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plantar warts occurs between the ages of 15 and 20 years.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of plantar hyperkeratoses is important since treatment is often specific, varying from one condition to another. Common resemblance of these lesions leads to diagnostic error if they are not pared down as part of the examination. There are 3 features of a plantar wart to be noted after paring: (1) hyperkeratotic ring, (2) central mass of tightly packed vertical threads, and (3) punctate bleeding points in the central mass (demonstrated on deep paring). These findings may not be so obvious in the satellite lesions of the mother-daughter type wart.

The clavus, or localized corn, has a sharply demarcated, translucent core without blood vessels. The neurovascular clavus, usually excruciatingly painful, has a less clear central translucent area and is traversed, parallel to the surface, by blood vessels. In contrast to plantar warts and clavi, callosity, or callus, a diffuse or circumscribed pressure hyperkeratosis, shows no deviation of normal papillary skin lines after paring. The mosaic wart, which is localized to pressure surfaces of the feet, consists of tiny (1 to 3 mm.) coalescent warty cores exhibiting the characteristic perpendicular capillaries after paring; the total area of coalescent seeds is large and resembles a mosaic in outline. Plantar radiodermatitis tends to show: (1) scarring interspersed with islands of hyperkeratosis; (2) telangiectasis; (3) interrupted papillary lines; and (4) a diffuse border.

OBSERVATIONS

From February 1958 to December 1960, the policy practiced in the Duluth public schools in

the case of plantar warts was as follows: (1) At the beginning of the school year and at appropriate intervals thereafter, all students using the swimming pools and locker room showers were examined by the swimming and gymnasium instructors for evidence of plantar warts. (2) Any student with suspicious lesions was referred to his physician for diagnosis and treatment. (3) If the diagnosis of plantar wart was made, said student was barred from the use of the school swimming pool, showers, and locker rooms until he presented a signed statement from his physician to the effect that the physician no longer considered the lesions infectious. This policy was instituted with the concurrence of the county medical society.

Some of the physicians to whom students were referred concurred with the diagnosis of plantar wart and did not treat the lesion in any way but still signed a permission slip for the student to reenter the school pools and showers. The perplexing question was: is the wart infectious and for how long?

In spite of strict observation of the regulations, with the exceptions mentioned, there was no lessened incidence of plantar warts in the group so regulated. A committee of representative interested physicians and school and county health officers recommended to the county medical society and the school board that such regulation be abandoned for a two-year period, during which time further statistical study and physician education about the plantar wart problem would take place.

Table 1 illustrates the reported incidence of plantar warts according to examinations by swimming and gymnasium instructors during the school year of 1959-60, when wart control measures were in force.

TABLE 1
INCIDENCE OF PLANTAR WARTS AS FOUND BY SWIMMING AND GYM INSTRUCTORS
(SCHOOL YEAR 1959-60)

<i>School</i>	<i>Total number of students</i>	<i>Male</i>	<i>Female</i>	<i>Estimated number of cases of plantar warts per teacher examination</i>
L	807	419	388	Negligible
M	198	116	82	Less than 5
O	739	371	368	57 (7.7%) Male 20, Female 37
S	199	108	91	0
WJ	1,339	659	680	99 (7.4%)
W	934	474	460	31 (3.3%)
WL	814	437	377	Not available

In an attempt to ascertain whether the use of school swimming pools had an effect on the incidence of plantar warts, 1,001 seventh and eighth grade students were examined by the author; 504 students were from a junior high school without access to a swimming pool, and 497 students were from a school with a pool and a regular program of swimming for all students. Table 2 illustrates the findings after a six-month period of no wart control measures. The examinations were made at the close of the 1961 school term. Swimming-pool exposure made little difference in the incidence of plantar warts. The students used comparable locker and shower facilities and probably represented families of the same socioeconomic level.

As part of the examination of the 1,001 students, the localization of the plantar wart on the sole of the foot was recorded. The areas of the foot were demarcated as described by Halberg.²¹ Figure 1 illustrates the incidence of plantar warts on a given sole area expressed in per cent of the total plantar warts observed in both schools. One or more warts within an area were counted as one localization for that area.

Figure 2 depicts the percentage incidence of total plantar warts on the Halberg areas, each single plantar wart being counted separately. There appears to be little percentage difference except for the heel area in the female, where multiple warts are common. The high occurrence in women of warts on the metatarsal head area, as reported by Rasmussen,¹⁸ is corroborated.

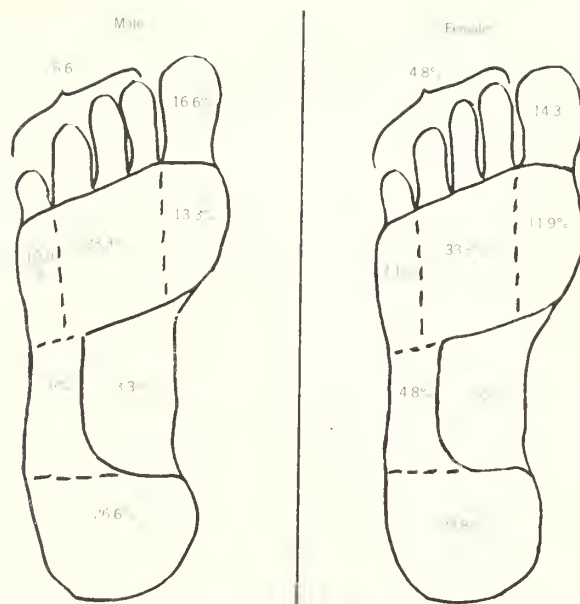


Fig. 1. Incidence of plantar warts on given sole areas in boys and girls (expressed in per cent of total plantar warts observed in 2 schools). Multiple localizations in one area counted as one localization for that area.

However, incidence of warts on the great toe area is not high. This variation from Rasmussen's finding may be due to the age group of patients represented by this study and the American schoolgirl's habit of wearing flat shoes.

A total of 660 students from the same schools was examined for extraplanar warts. Table 3 shows that 16 girls and 23 boys had extraplanar

TABLE 2
INCIDENCE OF WARTS AMONG STUDENTS FROM SCHOOL WITH AND SCHOOL WITHOUT SWIMMING POOL

	<i>School with pool</i>	<i>School without pool</i>	<i>Total</i>
Number of students examined for plantar warts	497	504	1,001
Male	266	255	521
Female	231	249	480
Number with plantar warts	28 (5.6%)	31 (6.2%)	59 (5.9%)
Male	15 (5.6%)	10 (3.9%)	25 (4.8%)
Female	13 (5.6%)	21 (8.4%)	34 (7.0%)
Right foot	14 (2.8%)	18 (3.6%)	32 (3.2%)
Left foot	12 (2.4%)	12 (2.4%)	24 (2.4%)
Bilateral	2 (0.4%)	1 (0.2%)	3 (0.3%)
Number of students examined for extraplanar warts	497	163	660
Male	266	88	354
Female	231	75	306
Number with extraplanar warts	26 (5.2%)	14 (8.6%)	40 (6.0%)
Male	15 (5.6%)	8 (9.0%)	23 (6.5%)
Female	12 (5.2%)	6 (8.0%)	18 (5.9%)

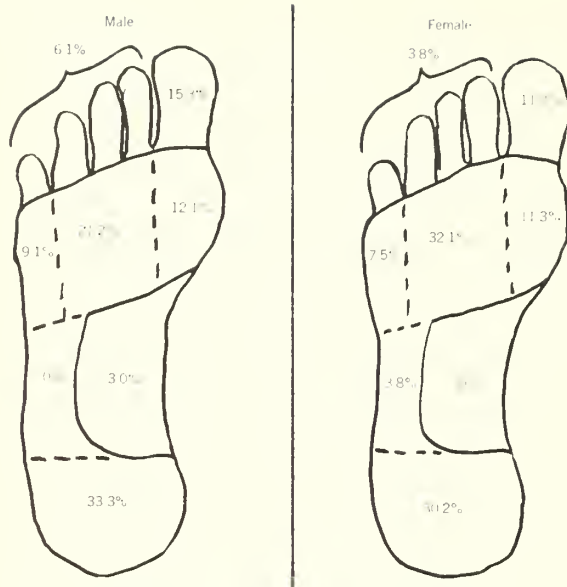


Fig. 2. Percentage incidence of total plantar warts on given sole areas in boys and girls of 2 schools. Each plantar wart was counted.

warts, nearly all being located on the hands. The preponderance of the localization on the right hand in men is noted, and this becomes more obvious when recorded as total number of warts. Bilateral and multiple warts were more common on male than on female hands. This also bears out Rasmussen's observation that extraplantar warts are not likely the source of infection for plantar warts, as men do not have correspondingly more plantar warts than women despite their higher incidence of extraplantar warts. In only 2 cases, both male students, of the 660 students were warts found on the hands and feet simultaneously.

SUMMARY

Totals of 1,001 and 660 junior high school students were examined for evidence of plantar warts and extraplantar warts, respectively; 5.9 per cent had plantar warts and 6.0 per cent, extraplantar warts. Plantar wart incidence did

TABLE 3
EXTRAPLANTAR WARTS AMONG 660 STUDENTS

	Females with warts	Number of warts	Males with warts	Number of warts
Hand	16	37	23	81
Right	7	15	10	52
Left	8	22	6	29
Bilateral	1		7	
Elsewhere	2	2	0	0

not increase during a six-month period without wart control measures in a school with swimming pool facilities. Attempted control of spread of plantar warts by elimination of wart-infected students from shower, locker, and swimming pools in one school did not lower the occurrence of plantar warts in the school. There was little difference in the number of students with plantar warts between schools with and without swimming pools. This finding differed from the increased incidence associated with pools reported by Rasmussen.¹⁸ If my statistical sample is valid, this leads one to suspect transmission of plantar warts at other places than school pools but presumably does not conclusively rule out school locker and shower rooms as a source of the rising number of students with plantar warts. Trauma to the site appears to have some bearing on the localization of warts on male hands and female forefeet. At present, there exists no known effective control measure to prevent spread of warts.

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Plantar Warts: "The Creation of the Devil"

A Practical Plan of Management

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Fargo

SOMEWHERE ALONG the line, plantar warts acquired the appellation, "the creation of the devil." The name is well deserved. Many a physician has been exasperated in his therapeutic efforts to eliminate these pesky lesions from the soles of the feet. Some physicians, shunning this vexing problem, urge plantar wart sufferers to seek help elsewhere. These "infections of minor importance"¹ loom large to patients and physicians alike. Unfortunately, not only are plantar warts recalcitrant, they are common. With some understanding of the causes, epidemiology, and other facets of the problem, every physician can formulate a therapeutic regime which assures a satisfying degree of success. To outline such a practical plan of management is the purpose of this essay.

CAUSES

The viral transmission of warts of all types is generally accepted. This was originally proved long ago by inoculation experiments.^{2,3} Later, the virus was visualized by electron microscope.⁴ Recently, the virus has been grown in tissue culture and has produced warts on reinoculation into human beings, thus fulfilling Koch's postulates.⁵ Still to be decided is whether one virus causes all types of warts or whether specific strains are involved in each type.^{1,6}

The wart virus presumably lurks in the dark and dank of locker rooms, school showers, and swimming pools. Exposure to such areas contributes to make the plantar wart incidence highest in high school age groups in the United States and Britain.^{7,8} On the other hand, in certain school districts of The Netherlands, where such school facilities are nonexistent, the incidence of plantar warts is remarkably low.^{9,10} Hence, this source of infection is apparent.

Yet not all persons exposed to such a milieu acquired plantar warts,¹¹ just as not all exposed to dermatophytes acquire dermatophytosis.¹² This fractional selectivity allows opportunity for spec-

ulation. With due regard to immune factors and other natural protective barriers, it is reasonable to assume that pathogenic organisms adopt as hosts only those individuals who provide a suitable terrain for growth. Paraplegics with anhidrosis show an extremely low incidence of dermatophytosis¹³ and no plantar warts.¹⁴ The wart virus does not find a dry sole suitable to its propagation and, if implanted thereon, cannot survive. On the contrary, a soft, moist foot becomes its happy hunting ground, and, having once located such a soil, the virus digs in and establishes domain.

There are undoubtedly a variety of reasons why people have moist feet, but 2 come to mind immediately. First of all, many people have natural plantar hyperhidrosis. Less well appreciated is the fact that many people, and this may be the larger portion, come by their moist feet unnaturally, so to speak. The ladies are aware that the wearing of nylon hosiery is associated with increased foot moisture. Whether such hosiery actually induces increased sweating or simply prevents evaporation of normal perspiration is immaterial. The result is a moist, warm foot.

Men and boys are not spared this health hazard. Nowadays, it is practically impossible to find a pair of dress socks made entirely of cotton fiber. Various percentages of synthetic fiber are mixed with cotton or the socks consist entirely of synthetic fiber. Stretch socks are the rage, as they "fit all sizes." The desirability of one's socks fitting all feet is open to question, but this is the sales pitch. With the incidence of plantar warts increasing in all parts of the world,^{7,11} contributing factors are being sought. The increased use of synthetic fiber in hosiery may well provide a clue.

Nor is this the whole story. The leather shoe, it would seem, has become a symbol of the ultra-conservative, while people who are "really living" hop around in rubber-soled canvas shoes. The popularity of tennis shoes among our high school and college populations would lead one to expect an imminent revival of that strenuous game.

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Then there are those persons, possibly manifesting rejection of a sedentary monotonous vocation, who "knock around" in engineer boots, cowboy boots, Wellington boots, and other inappropriate footwear conducive to increased foot moisture. The sympathetic physician must, with diplomatic suggestion, lead these people back to reality, humdrum though it be.

Since trauma and other mechanical factors have been incriminated in plantar wart causation, this emphasis on increased foot moisture may well be an oversimplification of plantar wart epidemiology. Be that as it may, recognition of increased foot moisture, whatever the cause, is essential in understanding and dealing with the plantar wart problem.

Prophylactically, men and boys should wear light cotton socks with a minimum of heel and toe synthetic fiber reinforcement. Women and girls should favor cotton-footed nylon hosiery. The heavy cotton sweat socks or bobby socks are contraindicated. Aside from the thick protective footwear demanded of certain occupations, the ordinary student and urban populations should wear light leather footwear with ventilation as the seasons permit. The impracticability of disinfecting public showers and swimming pool aprons is generally acknowledged. Hence, in such areas, the bare feet should be protected from contamination by the use of wooden clogs or plastic thong sandals.

EPIDEMIOLOGY

The behavior of plantar warts is baffling and frustrating. Sometimes, having eliminated a single plantar wart, the physician is dismayed to find 6 daughter warts popping up in the vicinity. The patients and their relatives are sometimes inclined to view the physician with suspicion, inferring that his therapeutic bungling has "spread the warts." The abashed physician, lacking an explanation, cringes in disillusionment and despair. Some of this bewilderment can be dispelled by a knowledge of the incubation period—or, possibly more correctly, the latent period—of the wart virus. Inoculation experiments have shown that the period between implantation of the virus and appearance of the wart may vary from several weeks to six, eight, or ten months or even longer.^{1,5} The reappearance of an ordinary wart at the periphery of an excision site two or three years after removal of the original wart leaves the definite impression that the virus has lain dormant all that time, to be triggered by factors unknown. The plantar wart discovered in February may well have been implanted the previous summer at the municipal swimming

pool, and the chances are that the daughter warts appearing today were incubating long before any therapy to the mother wart was initiated. Such knowledge, if it serves no other purpose, at least prepares the physician for these seeming calamities and provides a simple explanation for the hapless patient.

These unseen, or incubating, warts are to be reckoned with in any treatment program. In treating plantar warts with x-ray, I have gained the impression that unseen incubating warts provide strength, moral or otherwise, to the wart under attack, and, when all is said and done, the original wart frequently persists as a treatment failure while new satellites pop up in jeering arpeggio. Consequently, when further wart proliferation seems imminent—and this is indicated by the degree of moisture of the foot, the varying ages and sizes of existing plantar warts, the duration, and so on—it is often wise to defer a direct attack on existing warts, proceeding immediately with formaldehyde foot soaks, which will be described later, to dry the feet and thereby "turn the table" on the warts, seen and unseen.

EXAMINATION

As with all other disorders, the physician must precede therapy with a careful history and examination. Determination of the plantar wart status is best carried out with the patient lying face downward, outstretched on a full-length table. The physician, facing caudad, stands at or half straddles one side of the foot end of the table. The patient's foot may now be grasped in the physician's hands and brought up for easy visual examination. Positioning of the patient in a chair or supine on a table places the physician in an awkward examining and working position.

Next, the nature of the presenting lesions must be determined. Keratotic lesions on the soles of the feet are not necessarily plantar warts.¹⁵ Among other things, a punctate callosity must be differentiated from a plantar wart, a lesion for which it is commonly mistaken. The distinction is readily made by trimming away the surface hyperkeratosis. Punctate bleeding from exposed capillary loops is the hallmark of the plantar wart, while the central keratotic core of a punctate callosity becomes more and more translucent. A plantar wart is tender when pressed between the fingers (lateral pressure), while the punctate callosity is tender on direct downward pressure. Since punctate callosities are problems in their own right, it is not the intent to pursue this subject further.

In these days of expensive surgical equipment and elegant gadgets, it is gratifying that the

double-edged razor blade is still the most efficient instrument for paring away hyperkeratotic tissue. Cradled loosely between the distal phalanx of the right index finger and the middle phalanx of the right middle finger, a convex-bowed cutting surface is created by downward pressure in the center of the razor blade by the ball of the thumb. With a to-and-fro sawing motion, successive layers of keratin are shaved away until, in the case of plantar warts, beginning capillary bleeding is encountered. Such debridement clarifies the problem diagnostically, while the elimination of surface keratin allows more direct exposure of wart tissue.

Razor-blade trimming is carried out with the patient and physician positioned as described earlier. The physician may steady the patient's foot against his chest during this procedure, effecting a crude semblance of a blacksmith shoeing a horse. Better yet, an office assistant may steady the foot to prevent injury from any uncontrolled reflex jerking during the paring.

THE THERAPY

Having determined that plantar warts exist, the physician is confronted with a choice of therapeutic approaches. The textbooks and medical literature, replete with suggestions, confound the practitioner. The multiplicity of proposed treatments in itself testifies to the lack of a panacea. The treatment program about to be suggested is not a cure-all. However, it has much to recommend it. It is a simple procedure, readily carried out and offering an acceptable cure rate. More important, it minimizes the iatrogenic effects of some of the more enthusiastic therapeutic approaches. In general, excision, cautery, and other physical destructive procedures are contraindicated because of possible unpleasant sequelae.^{7,15} A painful scar on the sole of the foot must not be chanced. Radiation therapy requires special training of the operator and is limited in availability. Physicians, however, should not bemoan the general unavailability of x-ray therapy since this, too, leaves something to be desired, reported cure rates varying from 52.3 to 93 per cent.¹⁶

Briefly, the suggested method, a modification of that proposed by Epstein and Kligman,¹⁷ is as follows: (1) The wart is trimmed, after which trichloroacetic acid is applied. (2) This is blotted dry and tincture cantharidin is applied and allowed to dry. (3) This chemical remains in place, uncovered, for five days, after which time, depending on clinical indications, formaldehyde foot soaks may be instituted and employed until the time of the next office visit ten to fourteen days hence.

Trichloroacetic acid is purchased in crystalline form. However, since this substance is deliquescent, the bottle may simply be left unstoppered overnight while enough moisture is extracted from the atmosphere to change it into solution. Sophisticated persons or those in a hurry may bypass this chemical hocus-pocus by adding a few drops of water to produce a readily available solution. In such full strength, trichloroacetic acid may be applied with the end of a wooden applicator directly to the trimmed surface of the plantar wart. Needless to say, this produces an immediate painful stinging sensation, of which the patient should be appraised beforehand. The trichloroacetic acid is blotted dry after a few seconds, and a solution containing 0.7 per cent cantharidin in equal parts of acetone and flexible collodion is applied directly to the plantar wart with the end of a wooden applicator. Drying requires two or three minutes. Application should be confined directly to the wart and the solution should not be allowed to flow beyond its borders. The area is not bandaged.

The patient is instructed to leave the medication in place for five days without bathing the foot during this time. Subsequent office visits may be arranged at ten-day or two-week intervals and formaldehyde foot soaks employed during the interval between the expiration of five days and the subsequent office visit. The decision to use or not to use formaldehyde foot soaks is left to the physician and, as indicated above, is dictated by the degree of moisture of the foot and the impending threat of more plantar warts.

Cantharides (Spanish flies) are blister beetles. The active vesicating agent of these insects is cantharidin. Tincture of cantharidin (not cantharides) may be made up by a pharmacist, in the proportions mentioned above.* Since this solution is volatile, the bottle should be unstoppered only during the immediate time of application. However, should excessive evaporation take place, the solution can be restored by the addition of some acetone without materially affecting the potency of the medication.

The employment of cantharidin is not without some discomfort. The vesicating property of this chemical produces varying degrees of pain, starting several hours after application. The discomfort may last for a day or two. The response varies from patient to patient; some note little or no pain, while others complain bitterly. In an occasional instance, an anodyne may be neces-

*Cantharidin may be purchased from Inland Alkaloid, Inc., Tipton, Indiana. 1 gm., sufficient to make over 4 oz. of 0.7 per cent tincture, costs about \$3.50.

sary. Infrequently, a tense bulla may develop and require incision to relieve pressure. However, in most instances, the vesicating reaction is deep and diffuse without grossly apparent surface bullous response.

At the time of the return visit, in ten days or so, a dry, brownish crust is usually found at the treatment site. These desiccated crusts are trimmed off with a razor blade. Any apparent wart tissue remaining is again touched with trichloroacetic acid, dried, and treated with tincture cantharidin. The patient is again instructed to leave the medication in place, uncovered, for five days. Some warts are gone after 1 or 2 visits; others may persist for 3 or 4 visits. If obvious progress is not being made after 4 or 5 visits, this procedure should be abandoned and another considered.

Plantar wart proliferation can be discouraged and unseen incubating warts aborted by formaldehyde foot soaks. Formaldehyde not only reduces foot sweating^{18,19} but also, by its fixative action, produces a hard and dry sole, suggestive of one's having gone barefooted all his life. Such feet may not be acceptable to the aesthete, but not much, including plantar wart virus, will grow on such a terrain. Formaldehyde may also act to disturb the metabolism of the virus or disrupt a symbiosis of organisms which eventuates in plantar wart formation.

The formaldehyde foot-soaking procedure is a simple one, easily carried out by the patient at home. Formaldehyde, USP grade (37 per cent), is prescribed in 6- or 8-oz. quantities. The patient is instructed to dilute 1 part of the prescribed formaldehyde with 20 parts of tap water. Stronger or weaker solutions may be used, but this is a good starting dilution. The soles of the feet, involved as well as uninvolved, are placed in a glass or porcelain flat dish, such as a baking dish, and soaked in the diluted solution for twenty minutes daily, preferably in the evening before retiring. The patient should hold the feet quietly and not splash the solution over the dorsal surfaces of the feet. Since it is the intent to soak only the soles, the solution need not be any more than 0.5 in. deep. To allow ready access of the solution to the soles, a porous material such as a washcloth should be placed in the bottom of the pan.

After twenty minutes, the feet are removed from the solution and dried without rinsing. It is important to dry thoroughly between the toes, since any solution left in the interdigital spaces will continue to work and ultimately produce deep painful cracks which make further foot soaking impossible. Any cuts, cracks, or abrasions

on the feet preclude formaldehyde foot soaking because of the resulting pain.

If the patient finds it inconvenient to carry out this procedure every night, the strength of the solution may be increased to 1:15 and the soaking done for twenty minutes every third night. As a rule, this has less drying effect and is not as satisfactory as the daily procedure.

Patients who conscientiously and regularly employ formaldehyde foot soaks will be rewarded in several ways: (1) the soles of the feet become hardened and sweating is reduced; (2) new plantar wart development is largely or completely arrested and the impression is gained that unseen incubating warts are aborted; and (3) myriad plantar warts, presenting an almost impossible therapeutic problem, will occasionally dry up, turn brown, become crumbly, and flake off. When this happens, it is, of course, a pleasant and welcome surprise. Unfortunately, it occurs all too infrequently. In instances where many plantar warts exist, formaldehyde foot soaks offer a good initial approach to the problem, while treatment of individual lesions is withheld until the efficacy of formaldehyde foot soaking alone is determined.

An occasional patient may develop a pruritic papular eruption over the dorsal surface of the feet and on the lower legs, indicating the beginning of formaldehyde sensitization. In such instances, the procedure must be discontinued. Aside from the infrequent development of such sensitization, the foot soaks are generally well tolerated.

Of course, some people object to the formaldehyde odor. This was impressed upon me some time ago by the irate manager of a local movie theater. It seems that his theater was showing "The Bridge on the River Kwai," a popular offering which was breaking box office records. Suddenly, large numbers of people began to swarm out of the theater demanding their money back. Bewildered and dismayed, the manager elbowed his way through the outrushing mob. In the darkness of the theater he discerned an ever-widening black sea of empty seats. Persons in the exodus informed him that someone had dropped a "stink bomb." Suspecting foul play from his competitors or other unfriendly individuals, he called the police. Soon, detectives snooped about while the Fire Department laid down a covering of foam. The evening was ruined. The next morning, the distraught manager and his crew began to wash down the area with water, but the more they washed, the more unbearable the odor became. About this time, an employee announced that the same smell was

present in the ladies' washroom. There, rummaging around in the trash basket, these stalwarts came upon a sodden package in the wrappings

of a local pharmacy. Upon opening it, they found a broken bottle with the telltale label, "Dilute for foot soaks as directed."

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LUNG ABSCESES consequent to aspiration pneumonia may be prevented and surgical treatment of recent abscesses avoided by early penicillin therapy. Daily dosage of 1,200,000 to 2,400,000 units for at least three weeks is recommended. When bronchial obstruction is not associated, such treatment combined with proper postural or bronchoscopic drainage and supportive care usually is curative. Results are best when symptoms are of less than three weeks' duration. Patients with longstanding disease and residual cavities should be operated upon if medical treatment for three to six weeks is ineffective. In adults, the possibility of bronchogenic carcinoma must be considered. Review of 115 cases of lung abscess treated during 1943-56 indicates that (1) treatment has shifted from surgical to medical and (2) incidence of and mortality from the condition have been reduced greatly. Both changes can be attributed largely to use of antibiotics.

H. I. SCHWEPPE, J. H. KNOWLES, and L. KANE: Lung abscess: an analysis of the Massachusetts General Hospital cases from 1943 through 1956. *New England J. Med.* 265:1039-1043, 1961.

Nodular Cutaneous Elastosis with Cysts and Comedones

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THE TITLE "L'élastéidose cutanée nodulaire à kystes et à comédons" was used by Favre¹ and later by Favre and Racouchot² to describe a skin elastosis which had sufficient individual characteristics to differentiate it from similar but different forms of colloid-like degenerations of the connective tissue of the cutis.

The disease is not rare, but observers evidently have not considered it necessary to differentiate it from other closely related conditions. Degos³ lists "élastosis cutanée nodularis à kystes et à comédons" along with senile atrophy, colloid degeneration, diffuse elastomatosis of Dubreuilh, cutis rhomboidalis nuchae, and colloid milia under the heading of degenerative atrophies. There have been relatively few articles about the disease, and most of these have appeared in the French and German dermatologic journals. Many cases have been presented before continental dermatologic societies. We have been unable to find any articles or case reports in the American dermatologic literature except for one report by Sprecher,⁴ included by the editors of the *Year-book of Dermatology, 1958-1959*. Thus, this is the reason for this paper.

CASE REPORT

C. D., a 57-year-old man, had worked on a farm until age 40 but since then had worked indoors. He had been aware of curious lesions on the skin of his face and neck for many years. He had had acne vulgaris in his youth but had received no therapy. On the periorbital and temporal regions were numerous comedones supported by yellowish nodules. There were dense groups of comedones, tightly pressed together, simulating professional tattooing. Some of the comedones were small and pointed; others were more voluminous, of a blackish blue color, with thin, transparent walls. Extraction of such comedones would be very difficult, for the contents were dry and cottony and the surrounding friable epidermis was readily ruptured.

Among the comedones were nodules which were firm and resistant to the touch. Their color was rather light—

yellowish pink or sulfurous. Most nodules were associated with comedones; others stood alone.

The nape of the neck was marked with deep furrows which intercrossed, defining large areas of geometric contour, rectangular or lozenge-shaped. These areas themselves were divided by secondary folds or more shallow wrinkles. The skin was light yellowish pink, soft, and pasty. Comedones of variable sizes were seen, particularly in the folds but also distributed unequally over the areas which they limited. The comedones surmounted small nodules of a light yellow color. However, other nodules had several comedones, and some nodules appeared unassociated with comedo formation (figure 1 and 2).

Small cysts were prominent on the posterior surfaces of the external ears, also.

Using rotary dermabrasion, the cysts, nodules, and comedones were effectively marsupialized. This allowed adequate removal of the inspissated keratotic or cottony debris. Healing proceeded without complication and was complete after seven or eight days. Then the skin was still soft and slightly red but less pasty and relatively free from comedones, cysts, and nodules. This method was utilized successfully on the temporal and periorbital areas.

In addition to the use of light dermabrasion on small areas, sulfur lotion was applied, as in the treatment of acne.

DISCUSSION

Undoubtedly, experienced dermatologists have seen nodular cutaneous elastosis many times. Dr. Michelson directed my attention to it. It occurs most often in men past middle age and the influence of age is quite certain, yet E. Kunze⁵ recently reported 2 instances of the condition occurring in women aged 34 and 39 years, respectively.

Elastosis always develops on facial regions exposed to sunshine and weather—the cheeks, periorbital areas and lower eyelids, sides of the neck, forehead, behind the ears, and nasal alae. Cutis rhomboidalis nuchae may be present in the same individual. Other parts of the body have not been affected, according to the reports we have investigated.

The involved skin has an irregular surface, with a peculiar yellowish cream color. There are many small nodular cysts and a great many

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Fig. 1. Skin furrowed by wrinkles. Pale, firm nodules resembling colloid milia and pilosebaceous orifices are made more apparent by black dots of comedones.

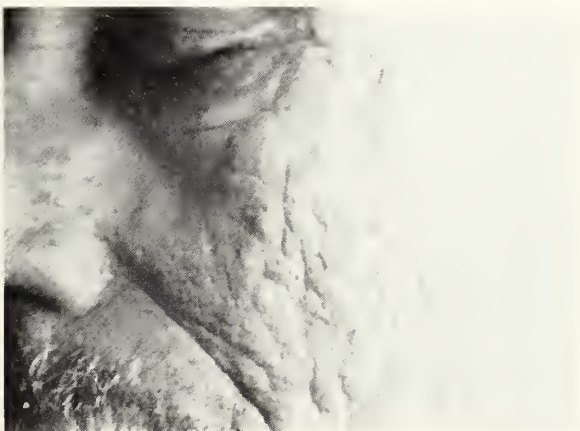


Fig. 2. Zygomatic area of cheek shows rugose surface of skin and association of comedones and nodules.

closely grouped comedones, which show no inflammation or suppuration. The comedones cannot be readily expressed, and slight pressure, as with a comedo extractor, readily ruptures the skin and produces hemorrhage into the tissue. If a number of cysts are punctured, some may exude a thick creamy substance, while others are apparently empty or dry.

Histologic criteria are subepidermal colloidal degeneration of the connective tissue fibers, formation of cysts, and comedones.

The question of the changes involved in the aging skin has received a great deal of attention. Unna accredited Neumann with the first investigations concerning senile atrophy. Jesionek tersely stated that senile atrophy was dependent upon chemical changes which represent nothing more than a corresponding stage in human age progression, which, of course, is constant and does not stand still. However, he conceded that atrophy may be an inflammatory phenomenon dependent upon foreign chemical substances.

Long-continued exposure of the facial skin to weather, with all its implications, has undoubtedly produced changes which have typified the so-called seaman's skin. But actinic rays must be the important factor in producing changes in the connective tissue. Lund and Sommerville⁶ confirmed previous reports that basophilic degeneration was limited to exposed parts of the body and that it increased in degree with age. The thin, keratotic, senile skin may vary the filtering power of the epidermis but, as Jesionek stated, the process is gradual, with the aging of the individual going hand in hand with the varying degree of protection derived from the epidermis. Then, too, there must be an accumulative effect of long-continued weather exposure with, possibly, a series of chemical reactions occurring more or less in sequence.

If a number of individuals with more or less similar skins live in the same physical environment for many years, their skins assume a similar hue and appearance. This is particularly notable in ranchers of the West, where the complexion might be called an occupational trademark. We mention this because nodular cutaneous elastosis is of unusual enough occurrence that it cannot be due to a common external factor, nor is it occupational in a broad sense, for the case reports include people in many walks of life.

Purpuric lesions found on the extensor surface and radial border of the forearm and on the back of the hand, not extending to the fingers, of people more than 60 years of age are of significance for consideration here. These lesions are dark purple, with sharply defined edges; the skin in the affected areas is smooth, inelastic, thin, and pigmented. Some lesions fade in a few days, while others last many weeks with little change. Tattersall and Seville⁷ found similar histologic changes in such cases. The epidermis was thinned and the papillae flattened; the collagen fibers of the dermis were reduced in number and replaced by elastic-staining fibers. These fibers stained less deeply than normal elastic tissue of the subpapillary plexus and were thick, tortuous, and fragmented. In some areas, the whole of the dermis was occupied by tangled masses of this abnormal tissue. Skin of the flexor surface of the forearm or from covered portions of the body showed no such abnormality. Other authors refer to this condition as actinic purpura because of the limitation to such exposed parts. It would seem that this concept disregards the role played by the combination of the aging process with sunlight in the development of such purpuric lesions.

Oil folliculitis, vaselinoderma, and other fol-

licular affections which have been definitely attributed to petroleum oils and chlorinated hydrocarbons are characterized by comedones occurring in other than an acne distribution. The similarity to oil affections has been mentioned in an effort to incriminate such oils as the cause of nodular cutaneous elastosis. Those of us who dealt with a tremendous number of cases of oil folliculitis in machinists and lathe operators during the war are able to differentiate quickly oil folliculitis from the disease under consideration because of the total lack of acute painful inflammatory and suppurating lesions which are so striking in the former condition.

We believe that oil applied externally, either in occupation or for cosmetic reasons, does not—in fact, cannot—produce nodular cutaneous elastosis. This condition cannot be interpreted either clinically or microscopically as being unintentionally or artificially produced. The marked degenerative changes take a long time to develop, and the epidermal changes apparently are secondary to this altered physiologic functioning of the cutis.

We believe, from our reading of various reported cases, that some of them undoubtedly were examples of oil-produced eruptions. In such reports, the histologic description could fit, for the criteria are not specific and the formula of comedones, cysts, and colloidal degeneration of connective tissue can be found in a number of conditions.

The morphologic description is, to us, the deciding factor—especially the xanthomatous color; the small, colloid milia-like papules; and the comedones appearing like small pegs driven into the ivory-colored little rings. There is no configuration, but there is decided bilateralism, not necessarily symmetric. Pressure on a fold of skin between the thumb and finger causes a thick, white, waxy material to exude, just as in some cases of acne, rhinophyma, and so on.

Histologic examination of the skin characteristically shows a thin, atrophic epidermis and numerous isolated cysts of unequal volume (figure 3). Some of these cysts are closed and buried in the derma; some communicate with the surface of the skin through narrow orifices of follicles, to which are attached stumps of pilosebaceous systems and normal or atrophic sebaceous glands. The cysts are lined with a flattened epithelium of malpighian cells. Some of the cysts are empty; others have a content of lamellae produced by the desquamation of the epithelium of the cavity. Occasionally, there is some indication of cavity formation in sudoriparous glands, with flattening of the glandular epithelium.

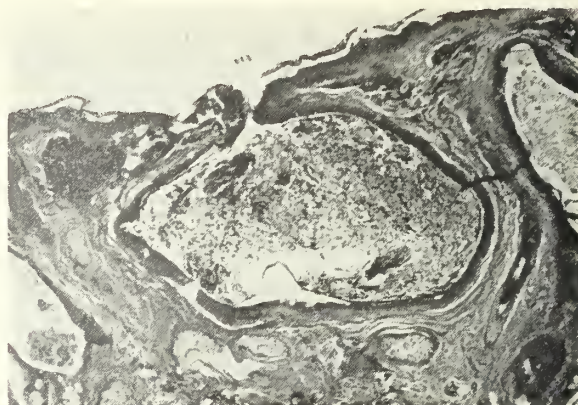


Fig. 3. Photomicrograph of thin, atrophic epidermis and large cysts with flattened epithelium, filled with keratinous debris. Compressed and displaced pilar sheaths and atrophic sebaceous glands. Dark-staining degenerative masses in upper dermis. Verhoeff's stain

The papillary portion of the dermis has large clusters of a degenerated substance separated from the epidermis by a thin band of normal dermic tissue. Elastic fibers and fibrils may be interspersed between the clumps. The degenerated substance is compact, thick, coarse, and without structure or forms globular masses. Although these masses have a marked affinity for elastic tissue dyes, they could hardly have been derived from the thin elastic network alone. The degenerative process must certainly involve the collagen fibers also. This abnormal material stains in the same manner as the elastotic material of senile skin, absorbing the elastic tissue dyes and failing to stain with the basic fuchsin of van Gieson's stain (figure 4).

The cause of nodular cutaneous elastosis is unknown. One may, we believe, eliminate a purely external physical cause by means of the history, the lack of inflammation, and the other elements besides comedones.

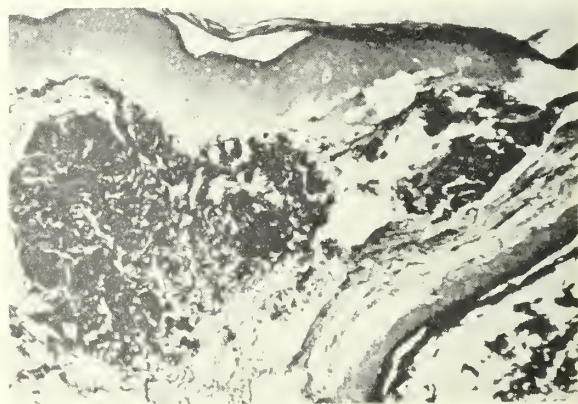


Fig. 4. Photomicrograph of degeneration of upper dermis intensely colored by elastic tissue stains. Verhoeff's stain

Aging alone does not seem to be an explanation, mainly because the condition is relatively uncommon and the development takes many years, so the condition really begins when the individual cannot be reckoned in the aged group.

The process of aging of the connective tissue of the cutis is a very complicated one and its discussion is beyond the scope of this paper, but the rather definite microscopic and tinctorial evidence is that of a degenerative process without manifestations of inflammation. The development of nodular cutaneous elastosis can be looked upon as an anatomic and physiologic defect. Since it occurs on the face and the epidermal changes include comedo formation, there is some connection with at least an acne diathesis. In a sense, it is analogous to the relationship of the rosacea state with rhinophyma—there are a great many patients with rosacea but only a few develop rhinophyma.

The soil, with its oiliness and patent follicles, offers the properties for development of this condition. Both the epidermis and the cutis develop abnormalities, so the entire integument must be the area taking part in the process.

No systemic abnormalities, such as diabetes, nephritis, and the like, have been shown to be associated with nodular elastosis. The patients are

apparently entirely well except for this progressive, unsightly, and intractable cosmetic defect.

The development and progress are a matter of years, and no secondary changes, such as keratoses or epitheliomas, occur, as have been observed in xeroderma pigmentosum. The cysts in nodular cutaneous elastosis do not resemble those found in epithelioma adenoides cysticum, nor are they reminiscent of syringocystadenomas. We do not believe the condition can be interpreted as nevoid in origin.

The author wishes to gratefully acknowledge the aid of Drs. Hamilton Montgomery and R. W. Goltz in reviewing the histologic specimens and preparing the photomicrographs.

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CAUSE of the defect in the pyloric myenteric plexus considered to be the primary factor in infantile hypertrophic pyloric stenosis is uncertain. Neither immaturity nor degeneration of ganglion cells could be clearly implicated or excluded in a study of 38 biopsy specimens of pyloric musculature from infants treated surgically for the condition and of 19 control specimens. However, no signs of advanced neuronal degeneration were noted in specimens from affected children. Such signs described in previous reports may have been caused by imperfect methods of preparing tissue for study.

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Benign Transitory Plaques of the Tongue and Buccal Mucosa

Review and Case Presentation

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BENIGN TRANSITORY PLAQUES of the tongue are known by many names, most common of which is geographic tongue, or lingua geographica, so called because of its maplike appearance. Depending somewhat on the variation of appearance, it has been called pityriasis linguae, exfoliatio areata linguae, erythema migrans, glossitis areata exfoliativa, glossitis superficialis migrans, and wandering rash. The latter was described as an entity in 1831 by Rayer. It has since been clearly recognized that these different appearances are all the same basic disease process.

DESCRIPTION

The lesions are generally described as circinate desquamations and involve the dorsal and, occasionally, the lower surfaces of the tongue. Only vague and infrequent reference is made to their location elsewhere. The lesions are circinate and superficial. They appear acutely and persist for a variable time, running a migratory course and then disappearing, leaving no postinflammatory or other residual changes. Ulceration does not occur. Usually, there are multiple, well-defined, gray, slightly elevated lines of superficial exfoliation which spread peripherally. The center of the individual lesion is red, shiny, smooth, and slightly depressed as compared to the elevated periphery.

The lesion continues spreading peripherally until it is about half an inch in diameter when it tends to resolve spontaneously. Often, neigh-

boring lesions coalesce, giving rise to more irregularly defined margins.

The time cycle for each lesion is from a few days to a week but may be longer. The condition is relatively asymptomatic, with only an occasional burning sensation associated with eating. It is usually discovered accidentally, and concern as to its significance brings the patient to a physician.

ETIOLOGY

The cause is unknown. Many factors are capable of producing change in the oral mucosa, both from local and systemic standpoints, but none can be definitely implicated here. Local dental hygiene has been suggested as a factor, but benign transitory plaques of the tongue have been reported in persons with good teeth. Psychosomatic implications have also been made. Winer¹ suggests excessive alkalization and infection of the overlying epithelium as factors. These may allow a keratinase to become more active. Black hairy tongue, on the other hand, produces an acid state and loss of the enzyme, resulting in accumulation of keratin. Occasional reference is made to the association of this condition with grooved tongue (lingua plicata).²

Children are more commonly afflicted, and there is a slightly increased incidence in women.

Microscopic examination of the lesions reveals parakeratosis, acanthosis, and an inflammatory infiltrate in the upper corium. The central portion is denuded. Scrapings show normal epithelium with parakeratosis in the white elevated areas.

TREATMENT

Treatment of this condition is not usually important, since it is often asymptomatic and is benign. Dental caries, if present, should be treated.

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Fig. 1. Lesion on buccal mucosa

Triamcinolone acetonide (Kenalog) was used in a series of patients with varying mouth conditions, 7 of whom had geographic tongue. In general, this preparation was useful in many other conditions but was of no benefit in the latter.³ Trypsin, a proteolytic pancreatic enzyme, has been suggested to help remove the serous exudates in mouth conditions, but benign transitory plaques of the tongue were not specifically mentioned.⁴

Often, relatively mild therapy, such as a bland mouth wash, is used. Kipping⁵ noted a case of benign transitory plaques of the tongue which had been present for fourteen years and cleared when the patient was given prednisolone for erythema multiforme.

CASE REPORT

A 20-year-old woman had noted migratory irregularities on the distal one-third of the dorsum of the tongue and buccal mucosa since 1958. These areas evolved in from three to five days and lasted about five to seven days. At times, they were only on the tongue and, at other times, only on the buccal areas, but they were usually present in both locations simultaneously. There were in intervals when the mouth was entirely clear. Except for slight burning, the condition was asymptomatic. The

patient was in good health, with no known dental abnormalities, and had taken no medications. There were no skin lesions elsewhere.

Examination of the tongue revealed the typical circinate areas, with a white elevated border and smooth central areas. The lesions on the buccal mucosa of the mouth (figure 1) were similar but had less central depression and peripheral elevation. Biopsy (figure 2) of a lesion from the buccal mucosa of the mouth revealed acanthosis with numerous small microabscesses containing many polymorphonuclear cells. The upper corium had these same inflammatory cells. In addition, there was considerable purpuric hemorrhage.

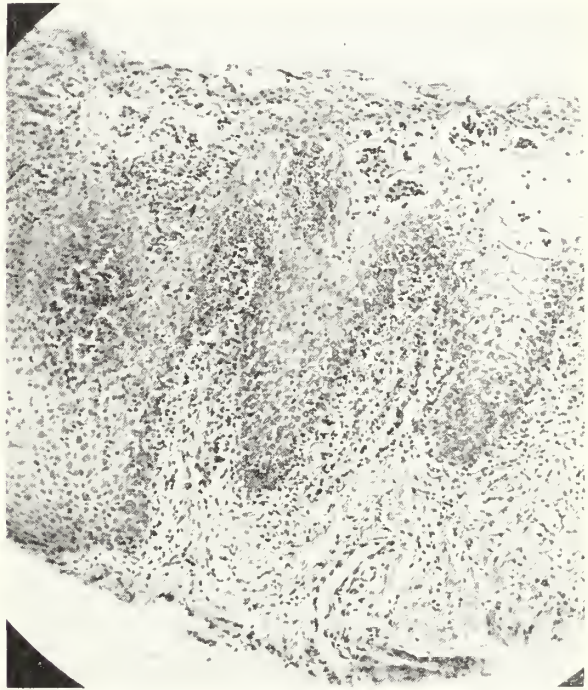


Fig. 2. Acanthosis, with numerous small microabscesses containing many polymorphonuclear cells

The reason for reporting this case is the unusual feature of the location of lesions elsewhere than on the tongue. No reference to a specific instance of lesions so located was encountered in the literature.

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Pemphigus Vulgaris

Re-evaluation of Management

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MOST MEDICAL practitioners recall the note of foreboding that accompanied a diagnosis of pemphigus vulgaris. Their brief exposure to dermatologic problems in medical school made them familiar with some of the difficult diagnostic and therapeutic problems. Pemphigus vulgaris, with its threat of an early death for the victim, was one of these conditions. Although the physician is unlikely to see many examples of this unusual disease, he is impressed with the clinical picture and prognosis.

To the dermatologist, new information and a different picture of pemphigus vulgaris have come within the past few years. In 1943, a new approach to the diagnosis was offered by Civatte,¹ who described histopathologic changes that have aided in differentiating the more severe from the milder of 2 bullous diseases seen in people of advanced years. Civatte called attention to characteristic histologic features of pemphigus vulgaris which permitted differentiation, even when difficult clinically, from the bullae of dermatitis herpetiformis and erythema multiforme. According to him, the primary change in pemphigus consists of the disappearance of the intercellular bridges in some areas in the epidermis. As a result, the epidermal cells lose their coherence with one another in a process referred to by Civatte as acantholysis. As a result of acantholysis, clefts form within the epidermis and cause disruption between the epidermal layers, thus forming vesicles or bullae between the basal layer and the rest of the epidermis (Fig. 1). As acantholysis progresses, there is detachment of the epidermal cells, singly and in clusters. These groups of cells lie free in the cavity of the bulla. The detached epidermal cells show loss of their intercellular bridges as well as other signs of degeneration. Their nuclei are swollen and spherical and their cytoplasm is homogeneous.

Civatte¹ found acantholysis and degeneration in all forms of pemphigus, including pemphigus foliaceus and pemphigus vegetans. He did not observe acantholysis in the bullae of dermatitis herpetiformis. In contrast to the bullae of pemphigus, these bullae were always in the subepidermal position, lacked acantholytic cells, and contained leukocytes and debris (Fig. 2). Frequently, eosinophils were found in large numbers.

Some writers earlier expressed disagreement with Civatte. Others have substantiated his findings and have enlarged upon them.^{2,3} In addition to the differentiation of dermatitis herpetiformis from pemphigus vulgaris, they separated a condition called senile dermatitis herpetiformis. A new classification was suggested—bullous pemphigoid.

Winer and Lipschultz⁴ found the subepidermal bullae in some pemphigus patients and intraepidermal bullae in others. Degeneration of the epidermal cells was observed only in the intraepidermal bullae. Similar observations were made by this writer. Rook and Whimster⁵ added to Civatte's report and made further suggestions for clarification and labeling.

The 2 distinct microscopic pictures have thus served to more clearly delineate pemphigus vulgaris. Bullous pemphigoid may have been completely removed from this serious-prognosis group. The tests of time and treatment will make for clarification. Pemphigus vulgaris with intraepidermal acantholytic vesicles occurs in a younger age group than does bullous pemphigoid. The disease tends to run a virulent course and still carries the same serious prognosis. Bullous pemphigoid with subepidermal nonacantholytic vesicles occurs in a somewhat older age group. The disease course is slower and milder and seems to be a lesser threat to the life of the individual.

Sanders and associates,⁶ in a recent review of therapy of pemphigus vulgaris, excluded this group of patients from their study of therapeutic

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Fig. 1. Benign pemphigoid

tic results. They state: "It is significant that none of these 20 patients (bullous pemphigoid) has died as a result of the bullous disease." There is no other review or follow-up on their patients. It is this writer's feeling that, though bullous pemphigoid is milder than pemphigus vulgaris, it nevertheless constitutes a difficult problem of management and does cause death on occasion. Similar intensive therapy is required for both pemphigus vulgaris and pemphigoid.

TREATMENT

The therapy of pemphigus, which at one time was strictly of the trial-and-error empiric type, has become more exact.^{7,8} With the inception of cortisone therapy, the course of pemphigus has been altered considerably. The prognosis is far better, with the survival rate elevated to various figures of 50 to 70 per cent. In some series reported in the past ten years, therapy has been centered on the use of ACTH combined with cortisone or either one alone. Without an accurate guide or index, the schedules have varied

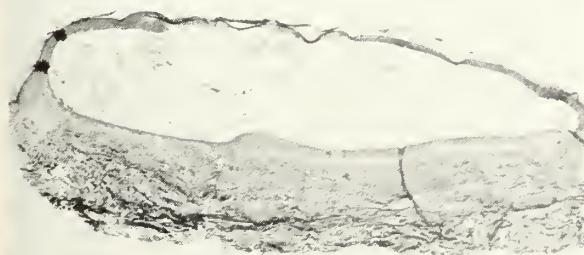


Fig. 2. Acantholytic intraepidermal vesicle

somewhat, but the end results have been similar. The important conclusion we can draw is that large initial doses are necessary to best bring the disease under control. Once under control, it is possible to gradually reduce the dose and in some cases to completely discontinue the drug for periods of time.

Reymann and Sobye⁹ rely upon treatment administered in repeated courses rather than on continuous therapy. The patient with benign pemphigus vulgaris, or pemphigoid, remained in remission much longer than did those with the malignant form. Of 7, 4 became symptom-free, as compared with 4 of 12 cases of malignant pemphigus vulgaris. Of their 19 cases, 8, including both types of histopathology, died.

In 1957, Costello and associates¹⁰ reported on the use of steroids in the treatment of 52 patients. In his series, the mortality rate was reduced from 90 to 33 per cent; 2 patients died of complications resulting from steroid therapy. The diagnoses in these cases were made by clinical course and microscopic picture of intraepidermal bullae with or without acantholysis. Mucous membrane lesions were found initially in 55 per cent of patients. Costello believes that the earlier the diagnosis is made in pemphigus vulgaris and the earlier the corticosteroid therapy is begun, the more favorable the prognosis. He feels that the disease is best brought under control by the use of high doses of corticosteroids initially. If necessary and urgent, 25 units of ACTH may be given intravenously in 500 to 1,000 cc. of 5 per cent dextrose slowly over a six- to eight-hour period. Costello also states a fact that has since become evident to us, namely, that the problem of management becomes greater in some patients when disease control is attempted initially with small doses.

All authors are agreed that the doses early in the management of pemphigus should be sufficiently large to control symptoms promptly. After symptoms are well controlled, dosage may be gradually reduced. Lever¹¹ agrees that the same schedule is often necessary in cases of bullous pemphigoid. Such an opinion underlines the thoughts of others that, despite the microscopic picture, the course of bullous pemphigoid is as serious as pemphigus vulgaris in many instances.

With the use of corticosteroids came the unwelcome physiologic effects of large and prolonged therapy, chief among which are cushingoid features, edema, mental symptoms, infection, moniliasis, gastrointestinal ulcer, glycosuria, heart failure, and osteoporosis.^{9,10,12,13,14} These effects have complicated the treatment and

caused death in some instances. Some authors state that most deaths in cases of pemphigus vulgaris are now due to the complications of treatment rather than to the disease itself.

A review of recently treated patients seen in 2 private dermatologic offices and 1 clinic practice yields similar impressions. It was the writer's feeling that pemphigus vulgaris could be differentiated from bullous pemphigoid only on a microscopic basis,¹⁵ since the clinical picture of the two diseases was so similar in a number of instances. For that reason, both conditions were evaluated together and therapeutic results were judged similarly. This was not a statistical report but an outline for management therapy.

There was but 1 death in the group, which occurred within one month of the original diagnosis and treatment. The patient was admitted with a severe generalized bullous eruption involving the entire body. Both the presence of mucous membrane lesions and the histopathologic picture of an acantholytic bulla established the diagnosis of pemphigus vulgaris. The eruption was well controlled and started to clear as a result of intensive corticosteroid therapy. On the twenty-fifth hospital day, the patient suddenly complained of severe lower back pain and went into shock. He died two days later with severe bacteremia. This death probably can be considered a complication of therapy rather than a result of the disease itself.

The remaining cases were roughly divided between those with acantholytic intraepidermal bullae and those with tension-type subepidermal bullae. Treatment in all instances was with corticosteroids. Other drugs may have been used initially in some instances, but, as they failed, corticosteroid therapy was begun. All cases came under good control. The effort was made to keep the patient comfortable without necessarily eliminating all cutaneous signs of the disease. With that in mind, it was possible to carry some patients along with small doses of steroids. In some instances, it was possible to discontinue specific therapy for long periods of time until an exacerbation took place.

In one instance, a 53-year-old man presented with bullae on his face and buccal mucosa initially. On the basis of the clinical and microscopic picture, a diagnosis of pemphigus vulgaris was made. The disease was well controlled with the administration of steroids. The patient remained on steroid therapy for a while but discontinued treatment and disappeared from observation for as long as two years in 2 separate instances.

Despite the lapses of treatment in a patient

with the microscopic criteria for malignant pemphigus vulgaris, this patient withstood his disease well.

Of this group, only 1 patient developed serious sequelae as a result of corticosteroid therapy. The others presented the expected cushingoid signs and the edema.

Two cases are cited here to point out the parallel between bullous pemphigus and pemphigus vulgaris.

CASE REPORTS

Case 1. A 56-year-old man (Fig. 3) was first seen in October 1953 with an extensive vesicular and bullous eruption involving the arms, legs, and trunk. There were no mucous membrane lesions. A clinical diagnosis of dermatitis herpetiformis or bullous pemphigoid was made.

Laboratory examination. From October 1953 to April 1954, 7 biopsy specimens were obtained from varying sites; 1 was reported as a possible pemphigus with intraepidermal vesicles but no acantholytic cells and the remaining 6 showed subepidermal bullae. In December 1954, still another biopsy slide contained a subepidermal vesicle.

Course. The patient was treated with large doses of sulfapyridine in October and November 1953. His cutaneous condition worsened, as did his general condition. His face and legs became edematous, and he lost weight in spite of the edema. The sulfapyridine was discontinued, and the patient was given 400 mg. of cortisone daily. He rapidly improved from both a cutaneous and a systemic standpoint, and the cortisone dosage was

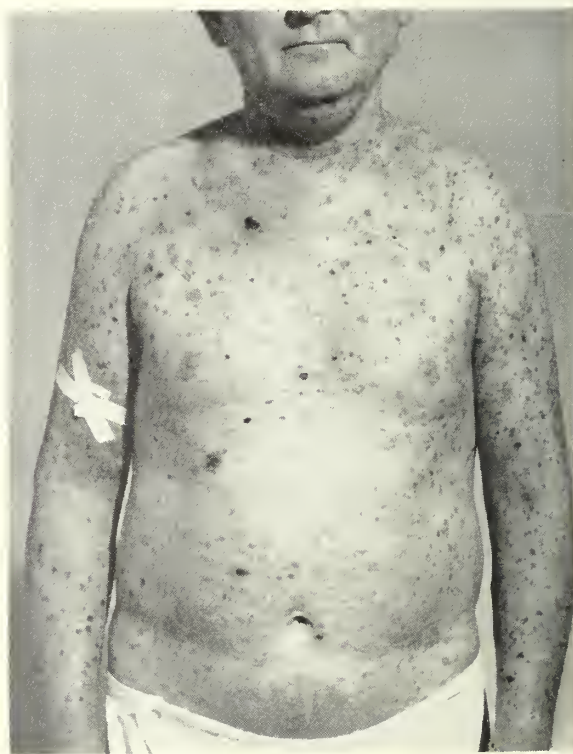


Fig. 3. Tension-type subepidermal vesicle

slowly reduced. The patient was followed at regular intervals from that time. In April 1957, he was readmitted to the hospital with severe edema of both legs and a stasis dermatitis, which slowly relented under appropriate hospital management.

In March 1958, the patient was given a different corticosteroid by his family physician. Shortly after initial use of that drug, a perforated peptic ulcer, which required surgical intervention, developed. Steroid therapy was discontinued rapidly, whereupon the patient's bullous eruption reappeared. The eruption was general, and again the patient's constitutional condition deteriorated, making it necessary to resume corticosteroid treatment. Therapy with prednisone (Meticorten) was reinstituted, and the cutaneous eruption again improved.

It has been necessary to maintain the patient with corticosteroids and a strict ulcer regimen since that date. The pemphigoid condition is well controlled. Roentgenographic examination reveals general osteoporosis, and the patient has evidence of wedging of the eleventh and twelfth thoracic vertebrae.

Case 2. J. N., a 65-year-old woman, was first seen in July 1958 with an extensive vesiculobullous eruption of one year's duration. The process first appeared under the breast and rapidly became extensive. During the first year of her disease, the patient had been treated with local medications only.

Examination revealed a severe general vesiculobullous eruption that was most concentrated in the inframammary, cural, medial thigh, and lower abdominal regions. There were erosions on the palate and buccal mucosa.

Laboratory examination. A biopsy specimen obtained in July 1958 contained an intraepidermal vesicle with

acantholytic cells. Blood counts and blood chemistry studies were normal.

Course. Therapy was begun with 8 mg. of methylprednisolone four times daily. The eruption rapidly came under control, and the dosage was reduced. The patient's weight, blood pressure, and electrolyte balance remained normal. At present, this patient with pemphigus vulgaris is being maintained on a dosage of 4 to 8 mg. of methylprednisolone a day and is in good condition. She shows no evidence of undesirable effects of steroid therapy.

SUMMARY

An accurate diagnosis of pemphigus vulgaris can be made more easily and a new entity has been separated from the group of pemphigus patients on the basis of histopathology.

The condition referred to as bullous pemphigoid appears among older patients and usually runs a milder course than does pemphigus vulgaris.

Both diseases require maintenance of large dosages of corticosteroids or at least repeated courses in order to control the cutaneous manifestations, as well as the disease itself.

The mortality rate of pemphigus has been reduced sharply.

Diagnosis in both instances is based upon histopathologic findings.

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Corticosteroids in the Management of Various Dermatoses

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THE INTRODUCTION of the corticosteroid drugs over ten years ago, associated with early favorable results, has stimulated their use in many recalcitrant dermatoses. Now, after a decade of experience, we are better able to appraise their therapeutic effects. In general, corticosteroids have induced marked alleviation of inflammatory and allergic reactions. Unfortunately, prolonged administration of these drugs has created complications that are often more debilitating than the original illness.

USE OF CORTICOSTEROIDS

Topical application and subdermal injection of corticosteroid medicaments produce few adverse reactions. The local effect is that of reducing inflammation and relieving pruritus. Their use is contraindicated only when infections are present. In these situations, steroids should be incorporated with an appropriate antimicrobial or fungicidal agent.

Nearly 100 topical steroid preparations are on the market.¹ We prefer the use of hydrocortisone in 0.25 to 1 per cent concentrations in most cases. Whenever these products are locally employed in acute or exudative eruptions or on lesions which involve the scalp or friction areas (axillas, feet, and groin), they should be incorporated in lotions or absorbent creams. When incorporated in a hydrophilic petrolatum base, hydrocortisone appears to be better tolerated by dry or more chronic eruptions. Also, other beneficial adjuvants may be added, such as epidermal stimulants—that is, tar and sulphur.

In recent years, we have been impressed by the results obtained by the local injection of steroids in chronic, local dermatoses. At present, subdermal injections or introduction by vibrapuncture technique² of prednisolone acetate³ or triamcinolone diacetate,⁴ in concentrations of 2.5 to 5 mg. per cubic centimeter diluted with 1

per cent procaine hydrochloride, is preferred (table 1).

Dermatologists have found increasing uses for the local application of the corticosteroids, and, generally, systemic administration of these compounds has decreased. Despite the introduction of newer and more potent drugs, serious complications remain a risk with prolonged utilization.

Prescribing steroids systemically, the physician must understand all the potential, adverse reactions and carefully and repeatedly observe the patient. At present, we prefer prednisone because it is less expensive and produces fewer serious complications. When muscle weakness occurs in patients with scleroderma or dermatomyositis, the triamcinolones should be avoided. In case of exfoliative dermatitis, which is secondary to psoriasis, this drug is more desirable.

Table 2 illustrates the comparative potency of these various compounds. One will note that 0.75 mg. of dexamethasone is therapeutically the equivalent of 20 mg. of hydrocortisone, yet each is similar in the production of undesirable side effects.

Systemic administration of corticosteroids is not curative but acts to suppress the clinical manifestations until the disease runs its course. If discontinued too early or decreased too rapidly, an exacerbation of the eruption occurs. Before instituting parenteral steroid therapy, the doctor and the patient must have a mutual understanding. When a physician decides that the disease will respond to steroids or is serious enough to warrant their use (table 3), he must make a careful examination to ascertain if any major contraindications (table 4) exist in this patient if the drug is to be utilized in excess of three or four weeks. The patient must be cooperative; return for frequent medical examinations (table 5); be aware of adverse signs, such as rapid weight gain, hemorrhage, and back pain; and always report the development of infection. The patient should be instructed to report the use of these drugs should an emergency develop.

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TABLE 1
RESPONSE TO USE OF CORTICOSTEROIDS
IN SKIN THERAPY*

Condition	Route of administration (response)		
	Oral	Intracutaneous	Topical
Alopecia areata	Good†	Good‡	None
Anogenital pruritus	RI§	Good	Good‡
Atopic dermatitis	Good†	Good	Good‡
Chondrodermatitis nodularis chronica helioides	RI	Good‡	None
Contact dermatitis	Good	Good	Good‡
Dermatitis herpetiformis	Good†	ID	None
Dermatomyositis	VR¶	ID	None
Drug eruptions	Good‡	ID	None
Erythema multiforme, severe	Good‡	ID	None
Granuloma annulare	RI	Good‡	None
Kaposi's sarcoma	None	ID	ID
Lichen planus, hypertrophic	RI	Good‡	None
Lichen simplex chronicus	RI	Good‡	Good‡
Local myxedema	RI	Good‡	None
Lupus erythematosus, systemic	Good‡	Good	None
Lymphomas	Good‡	Good	None
Mycosis fungoides	Good‡	Good	None
Necrobiosis lipoidica diabetorum	RI	Good‡	None
Nummular eczema	Good	Good	Good‡
Pemphigoid	Good‡	ID	None
Pemphigus vulgaris	Good‡	ID	None
Periarteritis nodosa	Good‡	ID	None
Pityriasis lichenoides et varioliformis acuta	Good‡	ID	None
Postherpetic neuralgia	VR	ID	None
Psoriasis	VR	Good‡	None
Pustular bacterid	ID	ID	None
Pyoderma gangrenosum	VR	ID	None
Sarcoidosis	Good†	Good‡	None
Scleroderma	VR	ID	None
Solar urticaria	None	ID	None
Synovial cysts	ID	Good‡	None
Urticaria, severe, acute	Good‡	ID	None
Xanthoma	ID	Good‡	None

*Modified from Stoughton, R. B.: Steroid therapy in skin disorders. J.A.M.A. 170:1311, 1959.

†Discussed in paper

‡Treatment of choice

§RI=rarely indicated

ID=insufficient data

¶VR=variable response

The dosage for any disease or patient must be individualized—the more severe the illness, the higher the amount prescribed. For general pemphigus or systemic lupus erythematosus, we suggest administration of 15 mg. of prednisone every six hours. If no therapeutic improvement

occurs in forty-eight hours, this amount is increased by 50 per cent every forty-eight hours until symptoms improve. The dosage is then slowly reduced by 1 or 2 tablets (5 mg.) a day until a maintenance level of 10 to 20 mg. per day is reached. We feel that a patient with pemphigus should be maintained on as small a dose as possible. A few lesions can be tolerated by most patients and complete disappearance of the eruption is unnecessary.

In less severe illnesses, such as drug eruptions or dermatitis venenata, the total daily dose seldom exceeds 40 mg. and is rapidly decreased to 20 mg. after four to five days. With improvement, this amount is further reduced by one-half tablet per day after ten to fourteen days of treatment. If exacerbations occur during the period of reduction, the daily dose is doubled until symp-

TABLE 2
RELATIVE ORAL DOSE OF VARIOUS CORTICOSTEROIDS

	Dose (mg.)
Cortisone	25.0
Hydrocortisone	20.0
Prednisone (Delta, Deltasone, Meticorten)	5.0
Prednisolone (Co-hydeltra, Meticortelone)	4.0
Methylprednisolone (Medrol)	4.0
Triamcinolone (Aristocort, Kenacort)	4.0
Dexamethasone (Decadron, Deronil, Gammacorten)	0.75

toms are again controlled. In chronic diseases such as pemphigus, this may occur episodically.

We seldom select these drugs for use in atopic dermatitis (table 3). Individuals with this condition are prone to become addicted, and complications, such as infections or mental aberrations, frequently develop. Only in the most severe exacerbations of atopic dermatitis do we utilize what we call the short-burst technic. Burst therapy begins with 20 to 30 mg. of prednisone in divided amounts daily for two to four days until edema, erythema, and pruritus are controlled; then the dosage is reduced by one-half tablet per day. We try to maintain these patients on 20 mg. a day or less for not longer than four to five weeks. Wet compresses, colloidal baths, antihistamines with acetylsalicylic acid, and topical steroids combined with tar or related compounds are effective and produce few complications.

In exfoliative dermatitis, a diagnosis should

TABLE 3
INDICATIONS FOR SYSTEMIC CORTICOSTEROID THERAPY

<i>Type of dermatoses</i>	<i>Specific conditions</i>	<i>Effect of corticosteroid therapy</i>
Severe refractory, ordinarily nonfatal, persistent, chronic or recurrent	Atopic dermatitis in severe exacerbation for short periods only Exfoliative dermatitis (always diagnose first)	Produces more rapid improvement during acute exacerbations when given over short periods
Ordinarily fatal	All forms of pemphigus Acute and subacute systemic lupus erythematosus Acute phases of dermatomyositis	Often effective; of limited value in treatment of acute phases of dermatomyositis
Severe refractory, ordinarily self-limited, acute	Eczematous contact-type dermatitis (severe generalized) Acute urticaria and angio-neurotic edema Certain drug eruptions (e.g., urticarial, purpuric, or bullous) Erythema multiforme (severe bullous type)	Often effective when given for short periods

always be made before starting steroids (table 3), as systemic steroid therapy will mask an occult lymphoma. Most cases of exfoliative dermatitis result from overtreatment of eczema or psoriasis. Our experience in management of psoriasis with triamcinolone has not duplicated those reported by Shelley and associates.⁵ We find that patients with psoriasis tend to develop complications such as cutaneous infections, septicemia, gastrointestinal perforations, hemorrhage, and thromboembolic episodes while on triamcinolone.

In table 1, various entities are listed and the best mode of steroid administration is indicated. In alopecia areata, systemic administration is usually effective; recurrences invariably occur after discontinuance of the medication. Prolonged therapy is always necessary and may be hazardous. Local injections of corticosteroids are effective. Dermatitis herpetiformis responds best to Sulfapyridine or sulfoxone sodium (Diasone). If intolerance to these drugs develops, steroids may be indicated. Lupus erythematosus, except for the systemic type, is usually controlled by the antimalarial drugs. Patients with sarcoidosis should receive steroids only when a vital organ such as the eye or heart is affected or the pulmonary vital capacity becomes greatly reduced.

Acute urticaria and severe cases of dermatitis medicamentosa are controlled by a "short burst" of corticosteroids. Short-term therapy is indicated whenever the problem is self-limited. The

TABLE 4
CONTRAINDICATIONS TO CORTICOSTEROID THERAPY

Active tuberculosis
Psychosis
Severe diabetes
Infections
Cardiac failure
Uremia
Virus diseases, that is, poliomyelitis, varicella, vaccinia
Active duodenal ulcer

TABLE 5
PRINCIPAL MEASURES TO BE INSTITUTED FOR PATIENTS RECEIVING SYSTEMIC CORTICOSTEROID THERAPY

Complete history and studies, with special reference to diabetes, hypertension, thrombotic or hemorrhagic states, psychoses, tuberculosis or other occult infection, and peptic ulcer

Weekly examinations during therapy: weight, blood pressure, urinalysis, and evaluation of course of disease, general symptoms, and physical and psychic states

Monthly examination when disease is controlled and dosage is under 20 mg. of prednisone per day or its equivalent

To prevent or manage complications: low-salt, high-protein diet with potassium supplement; antacids; and, when indicated, antibiotics, antituberculosis agents, testosterone and other anabolic agents, diuretics, and so on

TABLE 6
COMPLICATIONS OF SYSTEMIC
CORTICOSTEROID THERAPY*

Major
Adrenal insufficiency
Compression and other pathologic fractures
Hypertension (when severe)
Osteoporosis
Peptic ulcer (especially with hemorrhage)
Psychoses
Systemic intercurrent infection (tuberculosis, septicemia, and varicella)
Thromboses
Uncontrolled diabetes
Uremia
Minor
Acneiform lesions
Hirsutism
Hypothyroidism
Increased appetite
Mild glycosuria, hypertension, or both
Mild psychic changes (irritability, euphoria, restlessness, and insomnia)
Pedal edema
Petechial and purpuric skin lesions
Regional fat distribution (moon facies, buffalo hump, and supraclavicular fat pads)
Tremors and paresthesias
Furunculosis and pyodermas

*Modified from Sulzberger, M. B., and Witten, V. H.: ACTH and cortisone in dermatology. *Excerpta medica, dermat. ven.* (Section XIII) 9:1954.

use of steroids in chronic urticaria precludes prolonged administration, and, in our experience, side effects develop which are worse than the original disease.

Complications are divided into major and minor (table 6). The minor may be disconcerting to the patient but usually will clear within months after cessation of therapy; the major can become catastrophic, as exacerbations of infections with septicemia have been seen frequently after prolonged therapy. A recent survey at St. Mary's Hospital, Duluth, has shown a decided increase in active cases of tuberculosis during the past five years. A large percentage of these have received several months or more of steroid therapy. Hemorrhage from gastrointestinal

bleeding has been a frequent problem. Complications are serious enough to require the constant alertness of the physician because the euphoria of the patient will frequently minimize his symptoms.

Antibiotics should be used only when the need arises. Whenever the dose of steroids exceeds 20 mg. of prednisone daily, supplemental potassium chloride, 1 gm. twice daily, and antacids are prescribed.

SUMMARY

Topical and local subdermal injections of the corticosteroids at present offer excellent therapeutic applications when used as outlined. They are relatively safe, effective, easily used, and cosmetically acceptable.

Systemic corticosteroids have prolonged life in patients with fatal dermatoses. They have improved and allowed a more rapid return to normal function in many instances of self-limited acute dermatoses. These drugs are not curative but only physiologically effective in the reduction of inflammatory disorders. Unfortunately, these therapeutic benefits are counterbalanced by adverse physiologic effects which develop on prolonged or large doses.

The adverse reactions have been indicated and the methods for prevention enumerated. The physician must remember that, in most cases, steroids are intended for short-term use—five weeks or less; only then will complications and side effects be minimal. All patients must be constantly supervised, and alertness for all complications is paramount in the utilization of corticosteroids.

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Cutaneous Manifestations of Allergic Angiitis

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IN THE PAST few years, there has been increasing interest in a condition or group of conditions ranging in severity from mild, transient, cutaneous eruptions to severe, destructive, midline granulomas and the frequently lethal periarteritis nodosa. Despite obvious differences, these conditions have much in common, and the dividing line between them is not sharp. Their common denominator is a characteristic alteration in the blood vessels, which has been thought to be a reaction of hypersensitivity. For this reason, these patients have been labeled as having allergic angiitis, allergic vasculitis, or, in purely cutaneous forms, dermal allergid. Unfortunately, there is as yet no agreement as to classification of these conditions—or even whether they should be regarded as separate diseases or merely differing manifestations of the same fundamental disturbance. The purpose of this presentation is to review this subject, to present some illustrative cases, and to reexamine the questions of cause and classification of these disease states.

REVIEW

In order to better understand where our knowledge of this condition stands today, it may be worthwhile briefly to review its history. Periarteritis nodosa, the prototype of this group of diseases, was described as long ago as 1866. The diversity of the manifestations of periarteritis nodosa has always been unsettling to clinicians, and, in 1951, Strauss and associates¹ attempted to set apart from it the so-called allergic granulomatosis, which differed from periarteritis chiefly in that it occurred in allergic individuals and showed a greater number of eosinophils in its infiltrate. Along the same line, Zeek,² in 1952, split off from periarteritis allergic granulomatous angiitis and hypersensitivity angiitis, which was said to result from specific sensitivity to serum and drugs.

In the dermatologic field, Gougerot,³ in 1932, first described a condition which later came to be known as the “*maladie trisymptomatique*”

and, still later, as nodular dermal allergid.⁴ The “*trisymptomatique*” referred to the fact that 3 kinds of cutaneous lesions were present at the same time—small nodules, purpuric macules, and erythematomacular lesions. In some instances, however, the eruption was “*bisymptomatique*,” or even “*tetra-*” or “*pentasymptomatique*.” Fever, fatigue, arthralgia, and headache were sometimes present. Histologically, the cutaneous lesions showed the typical vascular alterations of allergic angiitis. Recently, Gougerot and Dupperrat⁴ concluded that “*maladie trisymptomatique*” is but one of a large group of cutaneous allergids—a group that also includes dermatitis nodularis necrotica, erythema nodosum, and rheumatic nodules. The condition is a mild form of a cutaneous allergic disorder, of which periarteritis nodosa is the most severe and lethal.

Ruiter,⁵ in 1952, independently described the same condition under the title of allergic cutaneous vasculitis. In subsequent discussions, he stressed that, in the last analysis, the diagnosis rests on histologic criteria and that classification of cases on the basis of relatively unimportant variations in clinical lesions is useless.

Judging by the number of reports in the literature, the various forms of allergic angiitis are being recognized more and more frequently by dermatologists.⁶⁻¹⁰ In 1959, McCarthy and Kesten¹¹ presented an intensive reevaluation of the subject and classified the cases into 3 groups, depending on the site and severity of the vascular involvement: group I was predominantly dermal vasculitis and included the conditions of Gougerot and of Ruiter, as well as dermatitis nodularis necrotica and pyoderma gangrenosum; group II was hypersensitivity vasculitis; and Group III was necrotizing angiitis with granulomas and included the allergic granulomatosis of Strauss and associates,¹ lethal midline granuloma, and Wegener's granulomatosis.

It will be remembered that, in addition to the dermatologic diseases mentioned, allergic vasculitis occurs in a number of systemic diseases and also in such experimentally induced states as anaphylaxis and Arthus and Shwartzman phenomena. The systemic conditions include the

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arteritis of rheumatic fever. It is interesting that, as long ago as 1940, Curtis and Pollard reported this type of vasculitis in Felty's syndrome.¹²

To summarize, we are dealing here with a group of closely related, if not identical, conditions involving either or both the skin and the internal organs. Despite obvious differences between the severe, even lethal, forms of the condition and the mild, purely cutaneous involvements, there is much overlapping in the clinical features of the reported cases. Whether we regard them as a series of different conditions or as variants of the same one ranging along a spectrum probably depends on our own inclination to be "lumpers" or "splitters." The common denominator is their histologic structure—more specifically, the characteristic angitis.

HISTOPATHOLOGY

As implied by the title, allergic angitis, the pathologic alterations in these cases center around blood vessels. The location and size of the involved vessels determine the clinical manifestations. In patients with cutaneous lesions, the vessels of either the dermis or hypodermis may be the seat of the disease, and both arterial and capillary vessels may be involved. Several distinctive features differentiate this type of vasculitis from ordinary inflammation (table 1). Notable is the swelling of the endothelium, which leads, in many instances, to complete occlusion of the vascular lumen. Perhaps as a result of this luminal obstruction, and also because of increased permeability of the damaged vessel walls, there may be extravasation of red blood cells, leading, in severe cases, to clinically visible purpura. White blood cells invade the surrounding tissue and, in the case of larger vessels, the vessel wall itself. The usual variety of cells is present, but notable, particularly in early lesions, is the large number of polymorphonuclear

neutrophils. Pyknosis and karyorrhexis of the nuclei lead to nuclear fragments, which are a striking and highly significant finding. Eosinophils, usually associated with allergic reactions, are inconstantly present. They may be completely absent or they may represent a large part of the infiltrate, especially in periarteritis nodosa.

Another striking finding is necrosis. There may be a cuff of necrotic connective tissue extending for considerable distances beyond the involved blood vessels. The necrotic tissue is usually basophilic and cloudy in appearance. The connective tissue fibers have lost their outline in these areas, and appropriate stains show the elastic fibers to be absent. Another finding may be fibrinoid degeneration, which consists of deposition of eosinophilic material, perhaps coagulated ground substance, between the connective tissue fibers, in the vessel wall itself, and sometimes in the lumen, contributing to its obstruction.

In addition to the changes in and around blood vessels, Allen¹³ reported some cases with epithelioid-cell granulomas. Other cases were characterized by large numbers of multinucleated giant cells, and another form was histologically indistinguishable from granuloma annulare and erythema elevatum diutinum. These may represent chronic forms of the disease, while the vascular lesions characterize acute forms. This is, in fact, the situation in rheumatoid arthritis, in which acute arteritis characterizes active phases of the disease, in contrast to the indolent and necrobiotic rheumatic nodules of late stages of the disease.

CLINICAL CONSIDERATIONS

If these vascular lesions are characteristic of allergic angitis, then any case with them must be seriously considered to fall into this group of conditions. At first glance, it would appear that such a group is highly heterogeneous, but the cases have many clinical as well as histologic features in common and may be etiologically related as well. The following is a more or less complete list of those forms of allergic angitis which have been reported to involve the skin.

1. *Periarteritis nodosa*, in the narrow sense—meaning those cases associated with characteristic renal, pulmonary, and other internal involvements. Cutaneous manifestations include a variety of papular, nodular, necrotic, purpuric, and ecchymotic lesions which can usually be diagnosed with certainty only by histologic examination.

2. *Allergic granulomatosis* of Strauss and associates¹—characterized by erythema multiforme-like, urticarial, hemorrhagic, and necrotic lesions and nodules. Systemically, pulmonary, vascular, gastrointestinal, renal, cardiac, and neural tissues may be involved. The resemblance to periarteritis nodosa is, to say the least, striking.

TABLE 1
HISTOPATHOLOGIC CRITERIA
OF ALLERGIC ANGITIS

1. Endothelial swelling, often leading to occlusion of lumen
2. Extravasation of red blood cells
3. Perivascular inflammatory infiltration, with preponderance of polymorphonuclear neutrophils
4. Pyknosis and karyorrhexis of the nuclei of neutrophils
5. Fibrinoid or basophilic necrosis of tissue surrounding involved blood vessels
6. Loss of elastic and collagen fiber outlines in necrotic areas

3. *Nodular dermal allergid* ("maladie trisympptomatique" of Gougerot, allergic cutaneous vasculitis of Ruitter)—includes cases with nodular, necrotic, purpuric, and erythematous skin lesions. Mild constitutional symptoms but not the characteristic lesions of periarteritis nodosa may be present. Again, it is obvious that there is no sharp line between this and periarteritis nodosa or allergic granulomatosis.

4. *Dermatitis nodularis necrotica*—included by some authors in the same group as nodular dermal allergid but having only one kind of lesion, a necrotic papule

5. *Pyoderma gangrenosum*—usually associated with ulcerative colitis. It is probable that the rapidly progressive necrosis in these cases is the result of vascular obstruction rather than a direct result of bacterial infection. The lesions are reminiscent of the experimentally induced lesions of the Arthus phenomenon. They have also been compared to those of the Sanarelli and Schwartzman phenomena, though this apparently has nothing to do with allergy.

6. *Lethal midline* and *Wegener's granulomas*—characterized by progressive destructive lesions beginning in the nose or lungs and with notable systemic symptoms. Death often results from renal disease. Cutaneous lesions consist of hemorrhagic, granulomatous, and ulcerative lesions.

7. *Purpuric states associated with protein disturbances*—include cryoglobulinemia, macroglobulinemia, hyperglobulinemia of Waldenström, myeloma, and so on. In addition to purpura, nodular and occasional necrotic lesions may be present.

8. *Anaphylactoid purpura* (Schoenlein-Henoch)—purpura results from local vascular reactions rather than from disturbances in bleeding and clotting mechanisms.

9. *Livido reticularis with ulcerations* (summer or winter)—histopathologic change is basically a vasculitis.

10. *Pernio*

11. *Erythema annulare centrifugum*

12. *Some erythema multiforme-like eruptions*—perhaps these fall into the first 2 or 3 groups above, but some cases difficult to distinguish clinically from ordinary erythema multiforme are characterized histologically by vasculitis.

13. *Erythema elevatum diutinum*

14. *Erythema annulare rheumaticum*

15. *Mucha-Habermann disease*—Szymanski has recently set this apart from chronic forms of parapsoriasis on the base of the vasculitis, which seems to be its prime feature histologically.

CASE REPORTS

The following reports represent a sampling of cases studied recently by members of the staff of the University of Minnesota Medical School. These cases were chosen chiefly because they present a variety of clinical forms of allergic angitis.

Case 1. An 87-year-old man had had recurrent attacks of an erythema multiforme-like eruption for a year and a half before examination. Cutaneous lesions were macular, nodular, purpuric, crusted, and sometimes necrotiz-

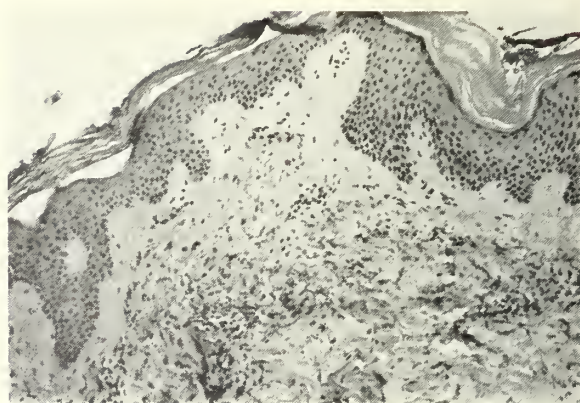


Fig. 1. *Case 1.* Extensive necrosis of connective tissue around involved blood vessels in subpapillary plexus. Hematoxylin and eosin

ing. They appeared in crops, persisted for two or three weeks, and subsided spontaneously. Their appearance was accompanied by fever as high as 103° F. Extensive studies showed no reason for the fever and eruption except a low-grade chronic urinary tract infection, from which streptococci were cultured. Other laboratory studies gave normal results except for an erythrocyte sedimentation rate of 103 mm. per hour and hyperglobulinemia—total serum proteins, 7.9 gm. per cent; albumin, 1.9; and gamma globulin, 3.5 gm. per cent.

Histologically, the cutaneous lesions showed an area of necrosis in the upper corium, leading to ulceration of the epidermis. The smaller blood vessels were occluded by endothelial swelling. Nuclear fragments were observed in the surrounding cellular infiltrate, and there was basophilic necrosis in the nearby connective tissue. Immediately beneath the epidermis, necrosis involved extensive areas of the corium (figure 1).

Case 2. A 7-year-old girl, whose final diagnosis was anaphylactoid purpura of the Schoenlein-Henoch type, had repeated episodes of an illness characterized by acute sore throat, fever to 104° F., abdominal cramps, vomiting, melena, migratory swelling of the joints, and an urticarial, infiltrative, purpuric eruption which appeared first on the legs and then spread to the arms.

Repeated tests showed the bleeding and clotting mechanisms to be normal. During active stages of the disease, leukocytosis was present and the erythrocyte sedimentation rate was 84 mm. per hour. There were also hyperproteinemia—8 gm. per cent—and marked elevation of the globulin fractions.

Microscopic sections of the skin showed the vessels of the deep and midportions of the corium, as well as those of the subpapillary plexus, to be involved. Present were luminal obstruction, karyorrhexis of the nuclei, and necrosis of the connective tissue characteristic of allergic angitis.

Case 3. A 45-year-old female physiotherapist had recurrent annular skin lesions in the pectoral region for about six months. The lesions began as erythematous papules which gradually enlarged and cleared centrally, forming annular and gyrate lesions 3 to 4 in. in diameter, with a raised, cordlike border and a flat, slightly hyperpigmented center. Oral corticosteroid therapy caused the lesions to disappear, but they recurred promptly when the drug was discontinued. General health was unaffected, and laboratory studies showed no abnormalities.

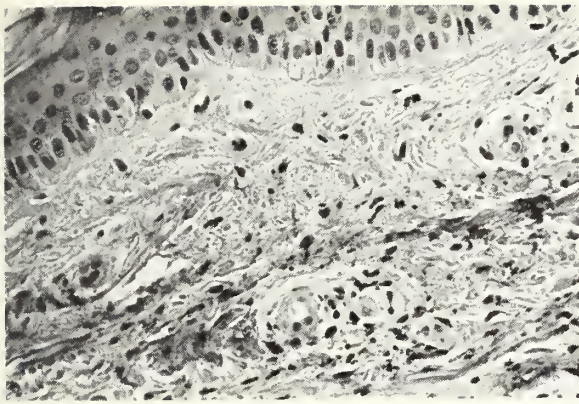


Fig. 2. *Case 3.* Occlusion of lumen of blood vessels by endothelial swelling was chief finding. Moderate necrosis of corium and extravasated red blood cells can be seen to left of vessel at bottom of photomicrograph. Hematoxylin and eosin

Dermatologic diagnosis was erythema annulare centrifugum.

Histologically, this patient's lesions showed less severe changes than did those of any of the other cases presented here. There was moderate perivascular inflammatory infiltration, with occasional fragmented nuclei and extravascular red blood cells. The chief change, however, was endothelial swelling, leading in some places to marked narrowing of the lumen (figure 2).

Case 4. A 58-year-old woman with a two-year history of parotid gland enlargement and recurrent episodes of purpura, chiefly of the lower extremities, provides an example of Waldenström's purpura accompanied by bilateral benign chronic enlargement of the parotid glands, or Mikulicz's disease.¹¹ In addition, she had systemic symptoms of pleural and pericardial disease and later exhibited signs suggestive of acute disseminated lupus erythematosus. Laboratory studies showed marked hyperglobulinemia, the globulin fraction being especially elevated, and a markedly accelerated erythrocyte sedimentation rate.

Histologic sections of the purpuric skin lesions showed the endothelial swelling and pyknosis of nuclei of allergic angiitis (figure 3). The parotid gland sections showed

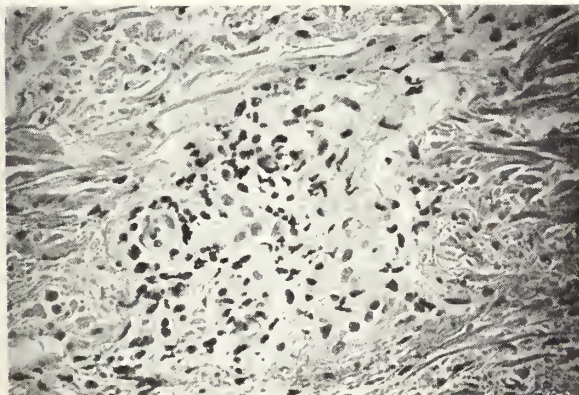


Fig. 3. *Case 4.* In addition to changes illustrated in figure 2, fragmentation of nuclei was striking in this case. Hematoxylin and eosin

the proliferation of the ductal epithelium and lymphocytic replacement of the glandular parenchyma characteristic of Mikulicz's disease.

Case 5. A 29-year-old man, 1 of 2 brothers with severe mutilating epidermolysis bullosa hereditaria, represents an example of Waldenström's purpura associated with epidermolysis bullosa dystrophica.¹¹ Both brothers had hyperglobulinemia, but only the propositus had purpura. His outbreaks occurred as a result of prolonged standing or exposure to cold and were confined to the lower extremities.

Histologically, this patient showed the most severe changes of this group. Figure 4 shows a middermal arteriole, the lumen of which has been completely occluded for a considerable distance. Surrounding it is necrosis, manifested by loss of cell outlines and dissolution of the elastic fibers.

ETIOLOGIC CONSIDERATIONS

As implied by the terms allergic angiitis and allergic vasculitis, there is a general presumption that immunologic phenomena play a fundamental role in the production of these disease states.

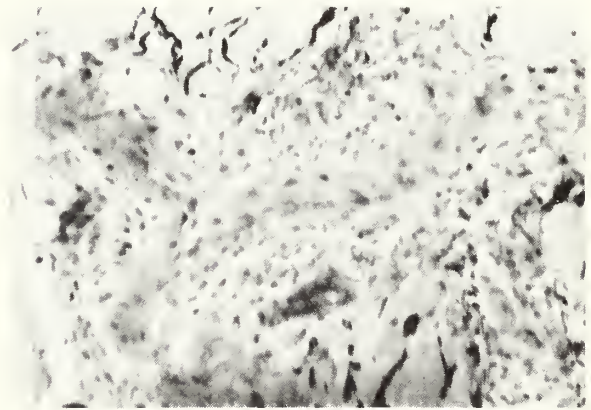


Fig. 4. *Case 5.* Complete obstruction of length of capillary lumen by endothelial proliferation and advanced necrosis of zone of surrounding connective tissue. Verhoeff's stain

A long series of clinicopathologic observations led to this hypothesis before there was any experimental evidence to support it. An example is the well-recognized fact that periarteritis nodosa may follow the administration of sulfonamides and probably represents a reaction of hypersensitivity to such drugs. This view was propounded almost twenty years ago in the classic papers of Rich. Along the same line of thought is the designation of hypersensitivity angiitis by Zeek.² Similarly, hypersensitivity to bacteria or their products has long been regarded as a cause of rheumatic fever and rheumatoid arthritis. Hypersensitivity to living organisms is recognized as a possible cause of those cutaneous disease states classified as dermal allergids. As noted earlier, such experimentally induced hy-

persensitivity phenomena as the Arthus phenomenon are characterized by vascular changes indistinguishable from those occurring in these disease states.

Recently, experimental work has been reported indicating that antigen-antibody reactions may be involved in the production of such vascular lesions. Dixon and associates¹⁵ demonstrated by fluorescent microscopy the deposition of antigen-antibody complexes in the vascular endothelium in experimental anaphylaxis, the deposition of fluorescent material occurring exactly at the point of thickening of the endothelium. Ishizaka and Campbell¹⁶ found that soluble antigen-antibody complexes produced increased capillary permeability in the skin of guinea pigs, a finding which may be of significance in explaining the purpuric lesions in patients with allergic vasculitis. The presence of antigenically active substances in the blood vessels of rats was shown by Pressman and his associates¹⁷ and in human endothelia, but not media, by Pionelli and his associates.¹⁸ However, as these authors have pointed out, this finding is not conclusive evidence that vasculitis is the result of an autoimmune mechanism, as some earlier authors maintained, but rather may represent a reaction of the endothelium with serum factors similar to that of rheumatoid arthritis.¹⁹

However, it remains to be proved that all instances of this type of vasculitis are the result of immunologic reaction, particularly since a variety of nonimmunologic agents, such as bacterial endotoxins, certain vasoactive drugs, and cold, may produce similar vascular lesions.

SUMMARY AND CONCLUSIONS

The cutaneous expressions of allergic angitis have been considered from the point of view of their history, histopathology, clinical forms, and probable causes. Five patients exemplifying various cutaneous expressions of allergic angitis have been described, together with their histopathologic findings. It appears that the funda-

mental disturbance in these conditions is a characteristic alteration in the arterioles and capillaries, which, in many instances, is produced by as yet incompletely understood immunologic mechanisms. While there are evident differences between the clinical forms which this abnormality may assume, nothing is to be gained by attaching separate names to all of its minor clinical variants.

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Gangrene of the Fingers in Lupus Erythematosus

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VASCULAR INVOLVEMENT in systemic lupus erythematosus is a constant finding but true gangrene of an extremity is rare. Klemperer, Pollack, and Baehr¹ described fibrinoid degeneration and sclerosis of the collagen as a fundamental change in lupus erythematosus. They emphasized involvement of the walls of arterioles. Montgomery,² however, was able to demonstrate little if any change in connective tissue in the walls of the capillaries and arterioles in the skin.

Schaffer, James, Scully, and Pillsbury³ in 1951 reported a case of a 27-year-old female with acute lupus erythematosus who developed multiple areas of gangrene of the digits, arms, legs, face, and ear lobes. The terminal phalanges of the toes eventuated in gangrene and mummification. Keat and Shore⁴ reported a case of a 14-year-old female with acute lupus erythematosus which demonstrated Raynaud's phenomena at first. Vascular involvement progressed to involve the toes, feet, and legs. Amputations were performed but death occurred shortly thereafter. In this case, large areas of necrotizing vasculitis, thromboses, and perivascular and intimal fibrosis were seen. The vessel changes were similar to those seen in polyarteritis nodosa.

Goltz and Smith⁵ also described vascular involvement in a case of lupus erythematosus, but in their case it was limited to recurrent ulcers of the leg.

Our case is presented to show profound and unusual skin involvement in a case of systemic lupus erythematosus.

CASE PRESENTATION

N.G.H., a 21-year-old Negro female, was first seen June 6, 1960, for exquisitely painful, ulcerated hands. About two weeks before her admission to Braekenridge Hospital, Austin, the process originated with a swollen, painful thumb which became vesicular and pustular and spread to involve all the digits of both hands. Increasing

ing cyanosis and blackening were noted after one week. There had been progressive hair loss and a faint eruption of the cheeks for six months. There was no atrophy of the skin.

Past history revealed an episode of almost total alopecia of the scalp and axillae in 1953 and 1954; however, the hair grew out again uneventfully until the present recurrence. In 1958, she was hospitalized for acute pericarditis of unknown origin. Lupus erythematosus test was negative at that time. In 1959, she had an abruptio placenta and delivered a stillborn fetus by cesarean section. There was no microscopic examination of the placenta.

Physical examination was essentially normal except for generalized, but incomplete, non-patterned alopecia of the scalp and a poorly defined, somewhat erythematous, slightly squamous eruption of the malar cheek areas (figure 1). The hands were clawlike and grotesque (figure 2). They were covered with deep ulcers, and denudation exposed portions of bone of several digits. Necrotic masses were evident at the periphery of the partially granulated ulcerations and the pungent, putrid odor was indescribably fetid.

Laboratory findings at the time of admission revealed significant abnormalities. A few erythrocytes were seen in the urine specimen. A test for coproporphyrin was positive; for uroporphyrin, negative. Hemoglobin was 10.4 gm. and the leukocyte count was 3,700. The sedimentation rate was 39 mm. per hour, corrected. The serologic test for syphilis and a sickle-cell preparation were negative. The lupus erythematosus test was positive, and many LE cells and rosettes were seen on a bone-marrow preparation. Blood protein electrophoresis revealed total protein of 7.2 gm. per cent. Albumin represented 2.3 gm. per cent (31.8 per cent), and globulin 4.9 gm. per cent (68.2 per cent): alpha 1, 0.33 gm. per cent (4.3 per cent); alpha 2, 0.6 gm. per cent (8.3 per cent); beta, 0.5 gm. per cent (6.8 per cent); and gamma 3.47 gm. per cent (48.8 per cent). Blood alkaline phosphatase was elevated to 7.2 B.U. and the serum potassium level was 3.3 mg.

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Fig. 1. (*Above*) A 21-year-old Negro female with acute systemic lupus erythematosus showing nonpatterned alopecia



Fig. 2. (*Right*) Same patient showing gangrene and ulcerations of the fingers

Cold agglutinins were positive in a dilution of 1:16. Bacterial cultures inoculated with debris from the fingers grew *Staphylococcus aureus*, coagulase positive, and a *Candida*, not *albicans*.

Skin biopsy specimen from the right forearm revealed atrophy of the epidermis, liquefaction degeneration of the basal layer, and scattered lymphocytes and plasma cells about the appendages and small vessels. Fibrinoid degeneration of the subepidermal area was demonstrated by means of the periodic acid-Schiff (PAS) stain.

The primary histologic changes seen in an amputated digit were vascular. There was a chronic necrotizing angiitis. Perivascular infiltrate of lymphocytes and plasma cells were seen primarily about capillaries.

Roentgenographic studies of the chest and an electrocardiogram were normal.

Her hospital course was somewhat stormy at times, although her temperature remained under 102.5° F. Treatment was primarily by means of corticosteroids. Methylprednisolone was started at 32 mg. daily along with corticotropin (ACTH) gel 80 u. daily. These were gradually reduced during her four-month hospitalization. Local therapy included wet compresses with a solution of Varidase and topical neomycin and novobiacin preparations. One attempt at split-thickness grafting to one denuded area resulted in

failure. Disarticulation of the right third finger was performed on September 21, 1960; however, healing of the amputation site required weeks.

When last seen in the spring of 1961, the patient was fairly well compensated but appeared chronically ill. Her hands had healed, leaving extensive scarring, deformity, and depigmentation.

CONCLUSIONS

Although it is well established that the blood vessels are consistently involved in lupus erythematosus, frank gangrene of the fingers and hands is an unusual development. Moreover, this manifestation was the singular reason requiring hospitalization on this occasion. This case only adds to the ever-increasing list of possible presenting signs and symptoms of lupus erythematosus.

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An Approach to Dermatologic Photography

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THERE is no other medical specialty which offers so many opportunities to the amateur photographer as dermatology. Certainly, no two patients present the same eruption. Indeed, if we consider for a moment that many thousands of patients have such a simple disorder as impetigo and that in each case the lesions are completely different, we then realize that there are unlimited opportunities to photograph these lesions, especially in color. At first thought, one might well say, "What is so wonderful about impetigo? It is a simple thing which responds readily to treatment." True, but once you begin to photograph these cases you will be startled by the great variety of morphologic changes in such a simple disorder.

As soon as you project your color transparency onto a screen, your little bit of impetigo is suddenly magnified to a beautiful true color photograph which will enable you to visualize and admire the multitudinous papules, vesicles, pustules, crusts, and bits of serous drainage that you had scarcely noticed before. You will be startled by the sudden realization that here, in this simple bacterial invasion of the skin, is a photographic panorama of skin pathology from simple erythema to the most profound morphologic changes. You will suddenly realize that there is far more to impetigo than a cursory look and a prescription for an antibiotic medication. Almost without realizing it, you will suddenly have the urge to become a student of details, rather than an observer of generalized skin changes.

If you will come with me into the exciting world of color photography, I will show you how to take these pictures so that you, too, can easily start your own library of skin disorders. Once you start taking photographs of your patients, the bug will bite you and never let go. As the Chinese proverb says, "A picture is worth a thousand words." You, too, will agree that your photographic records will tell far more than any-

thing you might write on the patient's chart. If your pictures are successful, and there is no reason why they can't be, you can quickly establish a voluminous collection of dermatologic slides and have fun doing it.

CHOICE OF CAMERA

If you have never taken photographs of dermatologic patients, your first question will probably be: "What type of camera is most suitable?" and the answer to this question is really quite easy. Since these are to be color photographs, they will almost always be shown with a projector and enlarged many times on a screen. Our choice of camera then rests between two different sizes, namely: the large twin lens reflex camera which forms its image on a $2\frac{1}{4} \times 2\frac{1}{4}$ -in. film, and the smaller 35-mm. camera which uses a $1 \times 1\frac{1}{2}$ -in. film. The former is an excellent camera and takes beautiful pictures, but it is designed more for situations where large areas are to be photographed or for action shots. Although it can be used to photograph the skin, it was not designed for close-up photography. In addition, its $2\frac{1}{4} \times 2\frac{1}{4}$ -in. slides are unnecessarily large and present quite a storage problem. We can pretty easily rule out this camera.

Let us then consider the 35-mm. camera. Here we have a camera which is ideally suited to our purpose and which has a high degree of versatility. Its small size enables one to use it in a minimum amount of office space, and when used out of the office, its size is such that it can be carried and used almost without effort. Its versatility is indeed remarkable. Not only is it ideal for close-up photography of patients and medical photomicrography but it can be used wherever one needs a camera for distance, close-up, or action shots.

Now that we have decided upon the size of the camera, our next problem is to select one from the many makes which are on the market. Since we would like to obtain exceptionally good pictures, our search should be directed to those cameras which are made to do fine work. One might draw an analogy from surgical instru-

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ments. One does not choose poor instruments, nor those which are cheap. Likewise, in order to get the best in pictures, one must get the best in cameras. You can't take good pictures with a poorly made camera. A fine camera is really a precision instrument and if we understand it as such, we will not hesitate to try to buy the best we can afford. It is difficult to single out one certain camera and to say that this camera is the best, and I do not wish to do so. However, I do want to mention the Leica as the one I have used for several years and which I have found satisfactory in every respect. There are 4 different Leica models to choose from and also a wide variety of lenses and other equipment so that, no matter which one you select, you can consider yourself to be in the middle to upper bracket as regards your camera and in an exceptionally fine position to do dermatologic photography.

As far as lenses are concerned, only 2 lenses are necessary and with them one can do almost anything photographically. The 50-mm. lens is the standard lens and can be focused as close as 19 in. to the patient and as far away as several feet. Thus, we can get close enough to take a section of skin 8 x 11 in. in diameter or we can move away and take as large a section of skin as we wish. When using the 50-mm. lens, the subject is brought into exact focus by means of the combined view finder and range finder. The subject is viewed through a single tiny window which is magnified so that the viewer has an excellent perspective of his field of view. If the image of the subject is out of focus, it will appear as a double image which can instantly be brought into focus as a single image by focusing the lens. In this way, the act of bringing the subject into perfect focus is simplified and does not require any special ability.

The real thrill in photographing dermatologic patients is in the use of the 135-mm. lens. This is a long focal length lens which can form a large image on the film from a tiny section of skin. It must be used with the bellows focusing device which allows one to vary the distance of the lens from the camera. When using the bellows focusing device the range finder-view finder method of focusing is not used. Instead, the Leica camera is converted into a single lens reflex camera by means of the Visoflex. This is an attachment which makes use of the camera's built-in range and view finders for focusing and framing the picture, but the subject is viewed directly through a ground glass. It is reflected into the ground glass directly from a mirror, so that there is no distortion of the field of view.

Accurate ground glass focusing is then obtained by moving the lens backward or forward until the subject is sharp. This distance between lens and camera determines the size of the image on the film and determines how near or far we may be from the patient. To illustrate: with the camera lens very close to the skin, the bellows would be completely extended, lens far away from camera, so that the lens could form a large image on the film from a tiny section of skin—that is, a true close-up showing individual lesions. On the other hand, if we move farther away from the skin to include a larger area, the bellows would bring the lens closer to the camera in order to include this greater skin area on the film and to have it in focus.

In addition to the proper camera and lenses, there are other accessories to consider before we are ready to take pictures. A tripod is a necessity because there must be no movement of the camera when the film is exposed. The tripod must be sturdy, so that it can easily support the camera and flash attachments, and adjustable so that it can be raised and lowered easily in order to quickly photograph areas on the upper or lower portions of the body. It would also be well if the head of the tripod could be locked into position easily by simply tightening the handle. The handle also enables one to turn the camera to either side or tilt it upward or downward without moving the tripod.

LIGHTING AND CHOICE OF FILMS

Fortunately, the problem of lighting is easily solved with electronic flash. These speed or strobe lights resemble natural light and have an extremely short duration of 1/5,000 to 1/10,000 second. This is a distinct advantage over older types of lighting because it eliminates glare which is so annoying to the patient in close-up work. With these units, the patient is hardly aware that the light has flashed. They are mounted on the tripod alongside the camera and are coupled with a built-in synchronizer within the camera so that the light flashes the moment the film is exposed. The length of the flash is such that pictures can be taken reasonably fast, usually 1/50 to 1/100 second, thus minimizing movement of the subject. The flash bulb is usually very close and attached to the camera so that the light is well balanced as it illuminates the subject. Thus, we need not worry about light distribution or shadows. As far as exposure is concerned, that will depend upon the intensity of the flash and the distance of the light from the subject. Each flash unit will have sufficient information so that one will quickly

learn after a little experience what the proper f stop of the camera should be. Since we are using electronic flash, the intensity of the flash will always be the same, so that the f stop will also be constant but will vary only with the distance. The closer the camera and light are to the subject, the less light is needed and the smaller the lens opening. On the other hand, the farther away the camera and light are, the more light is needed and the wider must be the lens aperture.

Although there are several different color films, the only one which accurately reproduces the natural colors of skin lesions is Kodachrome. Other films may have the advantage of greater speed but a high-speed film is not of any special value in photographing a quiet subject. One should select a film on the basis of its ability to reproduce color, not on its ability to take pictures at high shutter-speeds. The old Kodachrome with a speed index of 10 has proved itself to be admirably suited to every phase of dermatologic photography. It is still too early to make a judgment of Kodachrome II film. However, it appears that this film also portrays skin colors slightly better than old Kodachrome but that it does not show contrasting colors as well as the old film. If this is true, the old film will prove to be more effective since it is highly important that differences in color be pronounced. Otherwise, if there is too much blending of colors, the effectiveness of color photography is reduced.

Now that we know what equipment is necessary, we are ready to capture with our camera this wonderful panorama of dermatologic disorders which it is our privilege to see each day. But before we begin to snap our shutters, let us learn something of the art of photography. In order for our pictures to be outstanding, they must possess a high degree of interest, they must be properly composed, and they must have *impact*.

THE QUALITIES OF A GOOD PICTURE

One need not look far to find a subject of interest. Indeed, it exists in almost every patient. As an example, take such a simple thing as contact dermatitis. We see every degree of reaction from simple erythema to the most severe and prostrating form of dermatitis characterized by edema, erythema, vesiculation, oozing, and even secondary infection. Just think of the many wonderful opportunities to photograph this simple subject. Not only can we record the varying degrees of dermatitis but we can also take our pictures with respect both to the portion of skin

involved and to the offending substance. For example, we could select a substance such as oil and observe the different reactions oil has on the skin, such as contact dermatitis, chronic eczema, and oil folliculitis. These different eruptions could then be photographed, both from their morphologic point of view and their anatomic location. We could easily study the effect of petroleum products on the hands of various types of workers, compare these reactions on the skin, and, in this way, gain a more complete understanding of these various reactions. The same could also be done for oil folliculitis, in which a complete photographic library could be made of the action of oil and grease on the pilosebaceous apparatus.

Our pictures must not only have interest but must be properly composed. We would not have either pleasing or instructive pictures if we did not know how to compose them properly. That is, we must know how to arrange our subject so that the center of interest is placed in such a way that it will be the most striking part of the picture. In other words, it must have *impact*.

COMPOSING THE PICTURE

One can more easily understand proper placement of the subject by dividing the picture

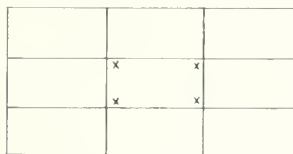


Fig. 1

frame into thirds (figure 1). The points of intersection of these lines are the strong parts of the frame, so that if a subject is placed in any of these positions, it immediately

commands the attention of the viewer in a much more forceful way than if it were either in the center of the frame or near the borders. Indeed, one must scrupulously avoid the exact center of the frame so that the subject will not have a target or bull's-eye effect. It is also important that the subject should not be too near the margins of the frame. The effect in these areas would be to have an unbalanced and distracting picture with too much extraneous skin area which is of no interest to the viewer. In a word, there must be a harmonious effect with the subject in one of the strong portions of the frame. This certainly need not be mathematically exact and one need not compose each picture by measuring the placement of the subject with a ruler. Rather, it should be used as a guide. To illustrate, let us suppose that we are going to photograph a case of pityriasis rosea. Since our picture is going to be a close-up, we should search for lesions of interest, and these

could be areas which are characteristic or those which are atypical. If we would wish to demonstrate the usual oval, erythematous, and slightly scaling lesions of pityriasis rosea, we might do

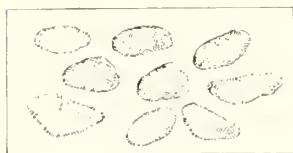


Fig. 2

nor does it have *impact*. Thus, by not being properly composed, it cannot command the attention of the viewer. How much better it would be if we were to move in very close and take



Fig. 3

the picture shown in figure 3. Here we have fulfilled all requirements of good photography. The picture is technically perfect, and, in addition, we have so composed the picture that the center of interest is obvious. In addition to showing the usual lesions of pityriasis rosea, we have shown a larger lesion, placed it in a strong point, and shown its relationship to the smaller lesions. In the first picture we are looking at a group of lesions, none of which can either dominate or hold our interest. On the other hand, in the second picture, we not only realize that we are looking at pityriasis rosea, but we are involuntarily forced to look at a single lesion. Both pictures have a similar number of lesions but only the second commands our attention. Although the center of interest was placed in the upper right third of the picture, it could just as easily have been in one of the other strong points and have been as effective.

THE CENTER OF INTEREST

In this connection, it is well to remind ourselves that the eye, in viewing a picture, does not immediately settle upon the center of interest. Unconsciously, our first glance is at either of the lower right or left corners. They are also known as strong points, not for placement of subject, but as areas which first command attention. From the corners, then, our eye rapidly and unconsciously searches for a center of interest. We can make this search easier and create a finer picture by composing in such a way that the eye is led directly to the center of interest. In figure 3, whether we realize it or not, the small lesions in the lower left corner quickly lead the

eye to the large lesion in the upper right strong point. Of course, it may not be possible to photograph every skin disorder in this manner, but it can be done in most instances. One need only spend a few moments searching for the right lesion or group of lesions that can be composed in this way. Again, to refer to figure 3, if the picture could not be composed in this manner, the camera could be moved slightly to the right so that the center of interest would be in the upper left corner. Here we have essentially the same picture, but the center of interest has been

moved (figure 4).

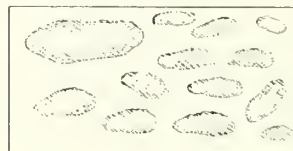


Fig. 4

Again, quickly and unconsciously, the eye moves from the lower right corner directly to the subject.

One can find a center of interest in almost every patient who has skin lesions. Consider any of the following: generalized dermatitis, psoriasis, lichen planus, urticaria, or erythema multiforme. These are all disorders which exhibit lesions that can be photographed in the above manner. To take a picture of generalized dermatitis it would be well, first, to move the camera back from the patient and take a portion of the body—that is, the general axillary area—in order to gain perspective. Then, to take a picture which has impact, move in quite close and concentrate on a definite lesion that will illustrate the case such as an area 1 to 2 cm. in diameter with a good deal of erythema, oozing, and crust formation. Place this in one of the strong points and, if your picture is technically perfect with regard to lighting and focus, you will have a strong picture that will tell your story in a dramatic way. The same is true for psoriasis. First, take a general view of a body area such as the knee or back. Then, move in close for one of the characteristic, or atypical, lesions 1 to 2 cm. in diameter, and place it in one of the strong points of the picture frame.

It may not always be possible to find a center of interest of the dimensions I have suggested. For instance, molluscum contagiosum exhibits lesions about 1 to 3 mm. in diameter, none of which are much larger. One should then try to find one or more individual lesions that are slightly different in that they would have more of a central plug or perhaps would have been scratched so that they would have a small crust of blood. Or, perhaps, one could find several lesions in a pattern such as a circle or a semi-circle. Any of these variations from the normal could then be placed in one of the strong points

of the frame to obtain a fine picture. The same would be true of insect bites. Scattered bites showing central punctum with surrounding hemorrhage or urticaria are probably not too interesting, but, if we can photograph these same lesions in linear or circular patterns indicating the path of the mite, we will have a picture which not only shows morphology but also tells a story.

Large solitary lesions are easily photographed, although one must be sure to place the subject properly. Since it is not possible to divide the frame into thirds and place the subject at one of the strong points, we can accomplish the same effect by having the lesion slightly off center and in the upper portion of the frame. This would apply to a large solitary plaque of psoriasis. In this instance, when we are trying to demonstrate one large lesion, we should avoid satellite lesions because they detract from our center of interest and we want the eye to rest on only one subject, not to be traveling around the frame looking at a bit of everything.

In this connection, we should be a bit more specific in focusing. When the camera lens is very close to the skin, a difference of only 1 mm. will place the subject in or out of focus. Very likely the section of skin we are going to photograph will not be equidistant from the camera at all points so that a portion of the lesion is bound to be out of focus. Our efforts, then, should be directed at only a tiny portion of the psoriatic plaque such as a small ridge or a bit of scale and this brought into focus. We should not concern ourselves with the entire lesion since it is virtually impossible to bring it all into focus. But if we concentrate on a tiny portion and place this minute area in a strong position, we will have a picture that fulfills all of the criteria which are so important. Our attention



Fig. 5

is drawn, not only to the plaque of psoriasis, but primarily to the ridge or scale which is in perfect focus. As another example, let us select an area of alopecia areata. Here again, let us search for a bald area which would occupy about two-thirds of the frame and then place it slightly off center (figure 5). As before, we should bring into focus a very small portion of skin showing the empty hair follicles. The surrounding normal hair would be out of focus because it would be closer to the camera. But this is of no concern because we are only interested in demonstrating the bald

area and to have the peripheral portions of the frame out of focus only heightens our interest in the subject.

THE VERTICAL PICTURE

Thus far, we have assumed all of our subjects to be transverse, that is, that their long axis is the same as the long axis of the frame. This is probably true in many cases but there will also be instances in which our subject will be vertical. It would be poor photographic technic to place a vertical subject in a horizontal frame because it would be impossible to place the subject in a strong position and have it all within

the frame. Thus, instead of having a pleasing picture as in figure 3, our picture would appear as is shown in figure 6. The center of interest

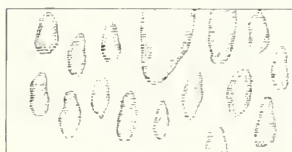


Fig. 6

is in a proper position but because its long axis is contrary to the axis of the frame, it is partially cut off. The obvious solution, then, would be to simply rotate the camera 90° so that the long axis of the subject is parallel to the long axis of the frame. Here again the Leica shows its superiority and adaptability. There is a very small knob on the side of the camera box which allows the camera to be quickly rotated without disturbing the electronic flash or tripod.



Fig. 7

if we rotate the camera, we thereby place the subject parallel to the long axis of the frame and again obtain a picture which satisfies all of the basic requirements of good photography (figure 8).



Fig. 8

What has been said for close-up work also applies to large body areas. In taking a picture of a patient's legs or thighs, we should not have the camera in a horizontal plane but in the vertical position. The same would hold true of the trunk as well as the head and neck. On the other

hand, the upper extremities may be photographed by having them extended horizontally

and having the camera in the same plane. But in photographing an arm or forearm one can go a step farther and, instead of having them per-



Fig. 9



Fig. 10

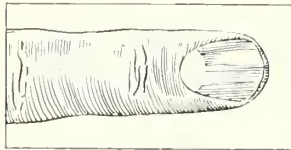


Fig. 11

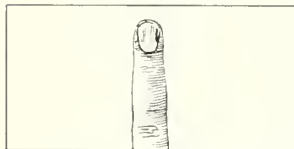


Fig. 12

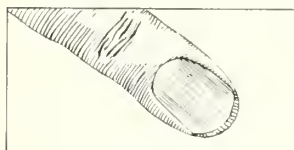


Fig. 13

fely horizontal, tilt them either upward or downward, as in figure 9. You can easily see that this is much more effective than if we had placed the arm or forearm in a perfectly horizontal position as shown in figure 10.

The same would also hold true for a finger. It should not be photographed as shown in figure 11 or in figure 12, but rather as shown in figure 13. Of course, in photographing such a small subject one should move in very close with the camera so that the finger will be greatly magnified and occupy as much of the screen as possible. Obviously, if it were not magnified, it would look quite ridiculous in an otherwise empty frame.

If there is ever any doubt about the proper relationship of the camera to the subject, a simple rule would be to use the position that will most easily include the entire subject, but at the same time remembering the rules of good composition.

ANATOMIC LANDMARKS

A picture which has been properly composed can be made still more attractive by including an anatomic landmark which can be easily recognized. For instance, in photographing a generalized disorder such as psoriasis, it is better to select a large lesion on or near a structure such as the hand, elbow, knees, or some other part of the body that is easily and quickly recognized. If the psoriatic lesion is on the elbow, the rules of good composition still hold. The center of interest should be in one of the strong parts of the frame but the exact position of the elbow itself need not matter too much. It could well be in either the right or left lower corner

so that it would lead the eye to the area of psoriasis. Of course, every picture will be different, especially its relation to anatomic structures. If we were to photograph an area of psoriasis on the dorsum of the hand we would attempt to place the center of interest in such a way that we could include the knuckles or portions of the fingers. Whether we are to photograph the elbow or hand, we are free to move them at will so that we may properly compose the picture. On the other hand, there are many other body areas that do not give us such freedom of movement. In these instances, we have to do the best we can and it may not always be possible to include a specific anatomic landmark. A solitary lesion such as verruca or an epithelioma on the side of the face may be too far away from either the ear, nose, or mouth to include them in the picture. Nevertheless, it is always well to keep this in mind and to try to include as much of these other structures as possible, but at the same time being sure that they are not too abbreviated. It requires judgment on the part of the photographer as to what may be included in the frame. A portion of the mouth might look all right in a side view of the face, but if only a part of the ear were included instead of the entire ear, the effectiveness of the picture would be lost because the ear would detract from the subject instead of complementing it.

The 3 most important anatomic landmarks for the photographer are the eye, ear, and nose. When these are properly placed in the frame the effect is remarkable, and the photographer who can find a bit of pathology in or near these structures is, indeed, fortunate. In the case of the eye, it must be level with the camera so that one does not look either up or down at it in viewing the picture. Nor should it be tilted to the right or left. In addition, the eye should be looking directly into the camera, the lids fully opened. And again, the camera should be as close as possible so that the eye will be greatly magnified and occupy almost the entire frame. Really, there is hardly a more attractive medical picture than a well-composed eye in which the eyeball, lids, lashes, and brows are in perfect focus and in which the colors are accurately represented.

The nose also lends itself well to close-up photography, not so much from a front view as from the side. Here, composition is easy—simply move in as close as possible and be sure to include the lower two-thirds of the nose. This view will demonstrate with great force any abnormality, especially a solitary lesion such as a basal-cell epithelioma. While one need not in-

clude the upper third of the nose, the same cannot be said about the lower portion. It is very important that the nostril be included in a lateral view; otherwise, the close-up of the nose loses much of its value. The ear should be photographed in much the same way as the nose. The camera should be in the same plane as the ear and the ear should fill the frame. As in the case of the eye and nose, the ear should not be tilted. In photographing the ear, it is difficult to bring the entire ear into focus because the various parts of the ear are not all the same distance from the camera. Therefore, as I mentioned earlier, focus sharply on the lesion or tumor which is to be the center of interest and do not be too concerned about bringing the rest of the structure into focus.

THE POSSIBILITIES OF THE CAMERA

Although a camera is a mechanical instrument, it is no more so than the instruments of a surgeon or the brush of a painter. In the hands of a surgeon, instruments hold the power of life itself, and, in the skilled hand of a painter, the brush can create a treasured painting. In the same way, the camera has the ability to create pictures which reflect the ability, knowledge, and imagination of the photographer. A simple case of impetigo means something different to

everyone who sees it. One observer might be impressed with the tendency of the lesions to involve the area about the mouth and nose. Another might be impressed by lesions in the scalp and ears. Still another would be intrigued with the morphology of the individual lesions.

Consider then, all of the photographic possibilities for each skin disorder as viewed by different photographers. One would photograph the area about the mouth, another the scalp, another would move in for a close-up of individual lesions, and so on. In the same way, psoriasis offers possibilities of photographing erythema, scale formation, pinpoint bleeding, Koebner phenomena, pitting of nails, heavily scaled scalp lesions, and arthritic joints. Each disease has its own characteristic lesions, its own predilection to involve certain body areas. What type of lesion or body area is selected must be chosen with care. One must not take a picture in an aimless way. The picture must reveal something characteristic or something which is unusual. This is not difficult to do and does not require special training. One need only know the technical requirements for good photography. Beyond that, reasonable knowledge of skin disorders, plus interest and imagination, are all that is required to open the door to a new photoramic vista of skin disorders.

PATIENTS with pulmonary infarction may have chest symptoms before peripheral venous thrombosis is evident. Often, such patients are in good health and are fully active immediately preceding onset of symptoms. Mistaken diagnosis of pneumonia may delay treatment with anticoagulants. Therefore, diseased leg veins in patients with equivocal chest symptoms should be regarded as potential sources of emboli. Likewise, the possibility of pulmonary infarction should be considered in active patients with atypical pneumonia symptoms but apparently normal leg veins, especially in subjects with frank hemoptysis. Of 117 patients with pulmonary infarctions, 13 had chest symptoms before venous thrombosis and 1 patient died without having leg symptoms. At onset of symptoms, 8 patients were apparently well and active, and illness simulated pneumonia in 9 subjects.

A. E. STEVENS: The late appearance of leg symptoms in pulmonary embolus. *Lancet* 2:1005-

Book Reviews . . .

The Spine: A Radiological Text and Atlas

BERNARD S. EPSTEIN, M.D., *second edition*, 1962. Philadelphia: Lea & Febiger. 616 pages. Illustrated. \$16.50.

Because of advances in the over-all knowledge of diseases of the spine, the author felt it necessary to edit the first edition of his text.

The basic format of the first edition, which was excellent, has been maintained and somewhat expanded by means of additional illustrations and the discussion of different entities. The quality of the reproductions varies from excellent to poor. Nevertheless, the title, *Atlas*, is misleading, for as such it is incomplete.

The embryologic and anatomic considerations are concise, well documented, and illustrated.

In spite of the fact that most known diseases affecting the spine and its contents are included in the text, emphasis is relatively uneven. The newer and therefore more interesting entities, such as metabolic and endocrine problems, are more frequently underemphasized when compared with the well-documented, familiar diseases. Likewise, illustrations of the newer and less familiar diseases are either inadequate or lacking.

The long-accepted procedure of myelography is overemphasized whereas discography is minimized due to the author's lack of experience with the procedure. In addition, spinal phlebography, a new and rewarding method of study of the spine, is not even mentioned.

In spite of its shortcomings, *The Spine* is a good reference for radiologists, neurosurgeons, orthopedic surgeons, and neurologists who are in need of a rapid and condensed version of innumerable spinal abnormalities.

SAMUEL B. FEINBERG, M.D.
Minneapolis

Psychiatry: Biological and Social

IAN GREGORY, M.D., 1961. Philadelphia: W. B. Saunders. 577 pages. Illustrated. \$10.00.

An author commonly submits a book for publication with some reserve and trepidation. On this point, among others, Dr. Ian Gregory of the University of Minnesota Medical School is notably and frankly different.

Dr. Gregory's book opens on a bold and lofty note. The following citation from the brief preface reveals his intents and purposes: "The theoretical orientation of this book is both holistic and eclectic, involving the integration of important material from various major schools of thought. It is intended to represent a balanced synthesis of American and European viewpoints, within the broad framework of both the International Statistical Classification and the Standard Nomenclature. It is designed to be concise yet comprehensive, scientific and systematic, descriptive and dynamic; to include both directive-organic and analytic-psychological approaches to treatment, and to integrate biological and psycho-socio-cultural research on etiology."

It should be noted that this field of theoretic and applied knowledge has been fairly well plowed before. Dr. Gregory's contribution, however, has a distinctive quality based upon his combined background of training in general medicine, psychiatry, and public health. The out-

come is a very excellent book, integrating the cumulative knowledge and experience of biologic science, preventive medicine, and psychiatry. The emphasis is on essential information, chiefly for medical students and general practitioners, and on critical evaluation of data with respect to scientific methodology.

Here, indeed, is a judicious, comprehensive, and sound digest of the diverse perspectives, principles, and practices prevalent in western psychiatry. Throughout the book, the author avoids doctrinaire blind spots and highly technical jargon. The contents of the book are appropriately divided into 2 main sections. The first deals with "General Principles," suitably presented. The next section deals with commonly encountered specific syndromes which are discussed in a practical and interesting manner.

The entire subject matter is well organized, highly readable, and clearly illustrated with explanatory and statistical tables. References to the literature are selective rather than exhaustive. The subject index shows special and sensible preparation. Medical practitioners, interns, residents, and postgraduate and undergraduate students should welcome Dr. Gregory's production as a helpful, handy textbook on biologic and social psychiatry.

P. J. SPARER, M.D.
Memphis, Tennessee

Rehabilitation of a Child's Eyes


HERBERT M. KATZIN, M.D., and GERALDINE WILSON, R.N., 1961. St. Louis: C. V. Mosby. 107 pages. Illustrated. \$3.75.

This book is written for the parents of children who have strabismus. The authors feel that a better understanding of the problem by the parents will result in greater cooperation and more effective treatment.

The first half of the book is devoted largely to visual physiology. The role of accommodation and convergence in producing squint is discussed adequately and is illustrated with diagrams. The authors point out the prominent part played by fusion. The role of heredity in the production of strabismus is covered well. The section devoted to birth injuries in the etiology of squint may have been overdone. This is especially true of a paragraph devoted to the proper application of obstetrical forceps. This paragraph adds nothing to the content of the book and may possibly pull the trigger on a malpractice suit, or at least cause ill will where it is not necessary. The authors give an excellent discussion of the psychologic aspects of strabismus and how this may affect the entire personality of the child.

The second half of the book is devoted to the evaluation and treatment of squint. The goal is to achieve good vision in both eyes, eyes which appear cosmetically parallel and which function together and are capable of binocular single vision or fusion. The tools the ophthalmologist uses to achieve these goals, namely, glasses, surgery, and orthoptics, are discussed. Orthoptic training is referred to as "eye exercises," and, although the authors are careful to point out that this involves training and learning, perhaps a more favorable connotation would result if some term such as "visual training" or

(Continued on page 16A)



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BOOK REVIEWS

(Continued from page 232)

"fusion training" had been substituted for "exercises." It should have been made clearer that formal orthoptic training demands good cooperation on the part of the patient and that such cooperation is not always possible in the early years when it would theoretically do the most good. In general, the discussion of the ophthalmologist's evaluation and treatment of squint is good. There are some who will disagree with such statements as "the child who is farsighted and whose eyes cross, where the glasses straighten the eyes partially or completely, should have his eyes re-examined under atropine at intervals of at least every six months" and "if fusion develops, there is a positive guarantee that the eyes will remain permanently straight." There are other rather dogmatic statements that will be easily understood by an ophthalmologist but not by a lay person.

In summary, the book covers the subject of squint in a concise and understandable language. While the words may be understood by the lay person, he will still be unable to assess their meaning in relation to his own child's problem. Because the lay person has not been trained to think like a doctor, the book would probably be more effective if fewer positive statements were made. An ophthalmologist who does not proceed exactly as the authors do may find himself questioned severely if the parents use the book as a score card.

ROBERT G. WOHLRABE, M.D.
Minneapolis

Medical, Surgical and Gynecological Complications of Pregnancy

ALAN R. GUTTMACHER, M.D., and JOSEPH J. ROVINSKY, M.D., editors, 1960. Baltimore: Williams & Wilkins. 604 pages. Illustrated. \$16.50.

This is a truly remarkable book. The New York Mount Sinai Group has, in addition to its obstetric staff, 10 specialty clinics to which complications of pregnancy are referred. This book is written by the men in charge of these complication clinics.

To a physician practicing alone in a community or to one seeking consultation from others practicing obstetrics in his area, the book is almost a must. Each complication is described briefly as to etiology, diagnosis, and management and is subtitled for easy reference. Unusually modern for a textbook and containing references which are for the most part available, this volume is a quick, brief, authoritative source of information on almost any obstetric complication.

To a teacher it should prove valuable; the text supplies the background information, recollection of original workers' names and references, and an easily organized format for use on teaching rounds. The book provides, usually without ambivalence, a philosophy against which we must consider our own deviations.

As is usually the case with such a book, the reviewer looks especially for answers to some of his unanswered problems. The answers may not be in this book. The discussion on management of "backache" provides the honesty, humility, common sense, and brevity needed to handle old problems with no new solutions. Some of the background material is statistically untenable as it exists in the original published form, but the reader is spared making a judgment on the validity of these references, since, wrong or right, the contributing editors have decided statistical issues from their personal experience.

With a reviewer's prerogative, I might suggest that hard black licorice is preferable to peppermint candy for the bad taste seen occasionally in pregnancy and that saccharated iron oxide, diluted 200 mg. in 250 cc. of 5 per cent glucose in distilled water and given intravenously, could be administered daily until the iron requirements are met. It is economical and practically devoid of side effects. However, further petty suggestions would only tend to dilute my high esteem for this book.

The chapters on heart disease and anemias alone would justify the inclusion of the book in every physician's library. Urologic complications, especially the common ones, deserve more space. The book is well organized, printed on good paper, and is recommended primarily as an excellent reference text for situations requiring rapid and expert opinion on obstetric complications.

JOHN S. GILLAM, M.D.
Fargo

The Roentgenological Aspect of Nonpenetrating Chest Injuries

JOHN R. WILLIAMS, M.D., and FREDERICK J. BONTE, M.D., 1961. Springfield, Ill.: Charles C Thomas. 135 pages. Illustrated. \$7.50.

This 135-page, solidly-bound text contains 8 chapters, 72 reproductions of roentgenograms, 4 charts, and an extensive bibliography of 341 articles.

The authors have done an amazingly lucid summarization of a large and difficult amount of literature. The reviewer found it distracting to find the bibliography referred to by the proper names of the authors rather than by number.

The selection and reproduction of the multiple roentgenograms were excellent for the depiction of the problems that were discussed. Roentgenograms having ill-defined lesions would have been enhanced by judiciously placed arrows; in fairness, the vast majority of the roentgenograms were so labeled. Several of the figures (6B, 20 A & B, and 21 A & B) were printed in such a manner that the reader had to turn the book to obtain a proper view. Such maneuvering proved disconcerting.

However, these are but minor criticisms. This is an excellent text, especially for practitioners who are involved in caring for patients with traumatic lesions. Its compactness and its extensive bibliography are complementary. The book should prove a splendid addition to the office library or to the emergency room of a hospital.

JEROME T. GRISMER, M.D.
Minneapolis

Problems in Surgery

FRANK GLENN, M.D., 1961. St. Louis: C. V. Mosby. 512 pages. Illustrated. \$16.50.

This unique volume, based upon tape recordings of the Grand Rounds of the Department of Surgery at the New York Hospital, Cornell Medical Center, presents 152 instructive cases covering almost all aspects of general surgery and the subspecialties. Problem cases in pulmonary, cardiovascular, gastrointestinal, plastic, orthopedic, urologic, and neurologic surgery are presented and discussed in terms of diagnosis and the different modes of management.

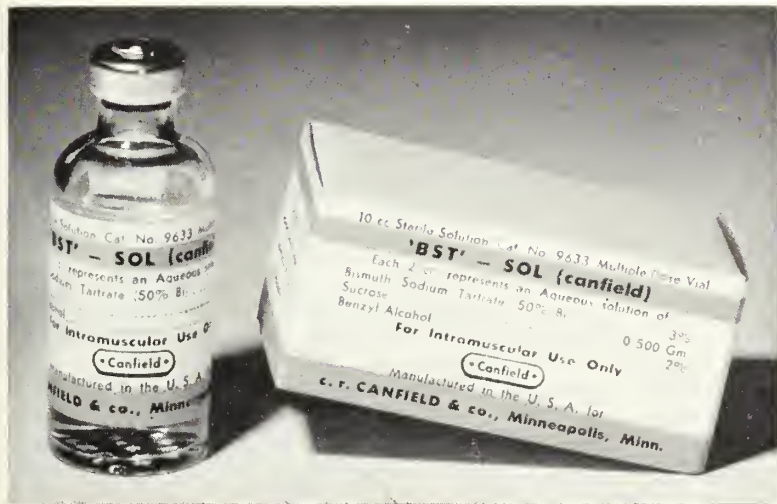
The participants include the senior members of the Department of Surgery, the 8 surgical subspecialties, representatives from anesthesiology, medicine, pathology,

(Continued on page 20A)

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BOOK REVIEWS

(Continued from page 16A)

pediatrics, and radiology, in addition to distinguished visiting professors from medical centers here and abroad.

This book reflects the informal and extemporaneous nature of the Grand Rounds and is effectively illustrated with numerous photographs, roentgenograms, and diagrams. Specific surgical techniques are also well reproduced. The various aspects of the problem in point are discussed with reference to the discussant's personal experience as well as those published in the literature. Pertinent, though incomplete, references are included at the end of each case. Cases presented for discussion are appropriate not only because of their complexity and rarity but because they may represent a relatively common problem.

Typically, each presentation begins with a history of a particular problem, followed by a discussion by the senior and visiting staff, and concludes with the decision and outcome of the case. The bibliography, though grossly incomplete, will probably give the reader a point of reference with which to start.

The excellent section dealing with problems in surgery of the alimentary tract is illustrated with 35 different cases. Chapter 5 on problems of the liver, biliary tract, and spleen is well done although surprisingly brief in view of the senior author's well known interest and contributions in this area. The section on fractures and dislocations is also superior.

Covering many problem areas, this book will provide an invaluable guide to the surgeon as a handbook of a logical approach to difficult cases in his practice. The volume should also prove to be a welcome addition not only to the young resident in general surgery but will also offer stimulating reading for the academician.

EARL G. YONCHIRO, M.D.
Minneapolis

The Adolescent Society: The Social Life of the Teenager and Its Impact on Education

JAMES S. COLEMAN, 1961. New York: Free Press of Glencoe. 368 pages. Illustrated. \$6.95.

Sociologist James S. Coleman of Johns Hopkins University is concerned over the increasing segregation of American adolescents into societies of their own. He sees them as "cut off from the rest of society . . . needing to carry out their whole social life with others their own age . . . speaking a different language . . . becoming an important separate market . . . focussing teenage interests, activities, and attitudes on things far removed from adult responsibilities . . . developing standards which may lead away from the goals established by the larger society."

Thrust into intense contact by the contemporary high school, which brings 90 per cent of them together daily (compared with 51 per cent in 1930 and 11 per cent in 1900), youth have developed a high level of social sophistication and a separate social system somewhat beyond the control of adults.

Coleman's book is devoted to showing how adolescent societies function. He includes a final chapter on how to redirect them. He feels that skillful redirection is possible and the only effective alternative to impotent exhortation of youth against the influence of their culture.

Most of his book is a clear and well-organized analysis, based on questionnaire responses from youth, their parents and teachers, and of adolescent cultures in 10 diverse communities. Among the topics explored are the prevailing values, attitudes, interests, and activities of

youth in each school, the nature of the leading crowd, what it takes to be popular, and the scholastic and psychologic effects of the adolescent social system. Instructive verbal and graphic comparisons illuminate differences among adolescent societies in small towns, big cities, and suburbia.

Coleman devotes most of his attention to group trends. He could make another substantial contribution by reporting on the many nonconformists who act counter to the trends. Neither adolescents nor methods of educating them will be fully understood until those who resist group pressure are given their due in research.

In summary, Coleman's book is imperative but incomplete reading for professional personnel who should understand adolescent social systems.

F. C. GAMBLIN
Robbinsdale, Minnesota

Clinical Laboratory Diagnosis

SAMUEL A. LEVINSON, M.D., and ROBERT P. MACFARLIE, M.D., sixth edition, 1961. Philadelphia: Lea & Febiger. 1,274 pages. Illustrated. \$15.00.

This sixth edition is a multiple author text which brings up-to-date advances in laboratory medicine as they relate to disease. Much of the text has been rewritten and several new chapters have been added. Subjects of the new chapters include viral and rickettsial disease and medical mycology. The chapter on hematology has been extensively rewritten.

Illustrations and color plates are generally of good quality. The chapter on hematology has several color plates. Especially noteworthy throughout the book are the 150 excellent tables on clinicopathologic correlations. Examples of these are a table on classification of enzymes and tables on inborn errors of fat metabolism, inborn errors of amino acid metabolism, and inborn errors of carbohydrate metabolism, all of these in the chapter on metabolism.

It is difficult to think of a laboratory procedure which is not discussed in this book. Of necessity, many subjects are discussed only briefly. For most chemistry procedures one method is given, with little attempt to discuss relative merits of various methods. Very little space is given to automation, which is playing an increasingly important part in the modern laboratory.

While some pathologists or residents in pathology may consider this book too brief in many fields, it is certainly a readily available reference for any laboratory procedure. It would be especially helpful in the laboratory or hospital library as well as to the physician in practice and the medical student or intern with an interest in the laboratory as it applies to clinical medicine.

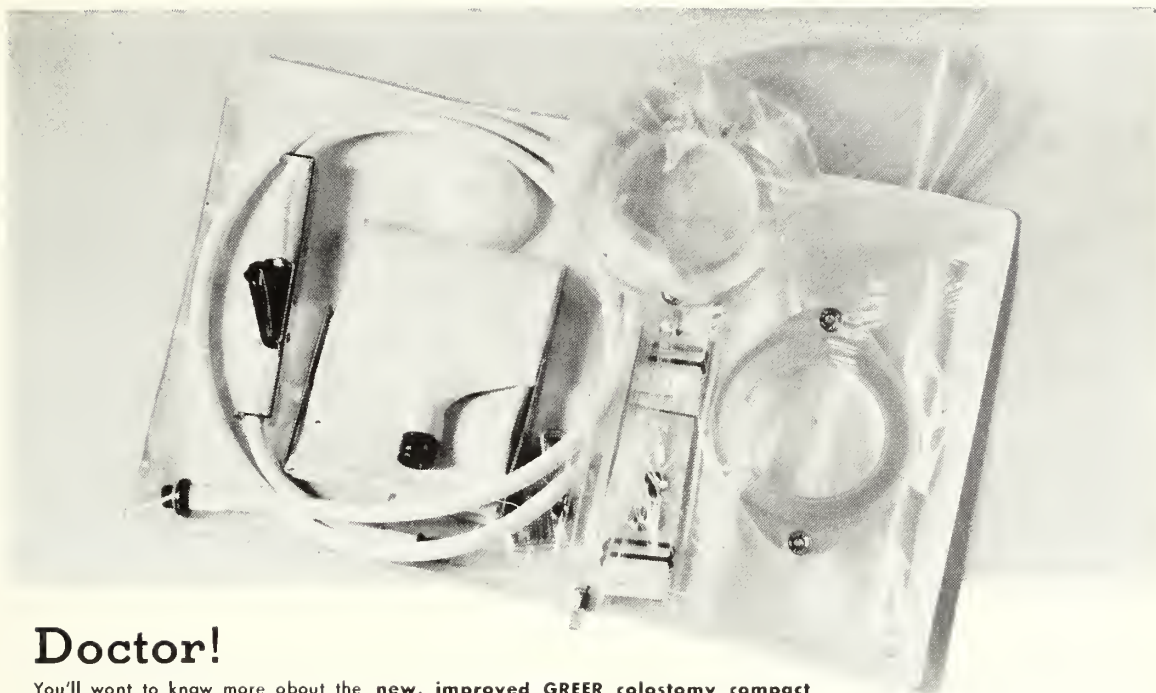
RICHARD P. LYNCH, M.D.
St. Paul

An Atlas of Pain Patterns

L. A. SMITH, N. A. CHRISTENSEN, N. O. HANSON, D. E. RALSTON, R. W. ACHOR, K. C. BERGE, and C. W. MORROW, 1961. Springfield, Ill.: Charles C Thomas. 54 pages. Illustrated. \$12.50.

This atlas depicts, in excellent colored illustrations, the points made in previous writings by the authors and emphasizes, in a dramatic fashion, the important points that have been made as to how pain patterns may be helpful in differential diagnosis. This atlas might well be used in medical schools to shorten a period of learning.

JOHN S. LUNDY, M.D.
Chicago



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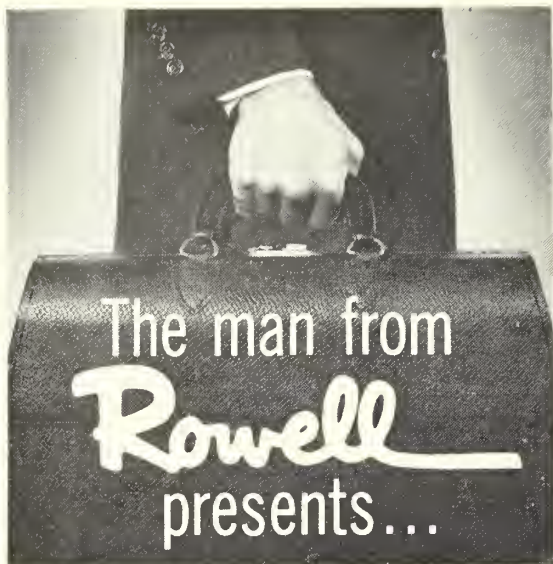
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News Briefs . . .

General

THE UNIVERSITY OF MINNESOTA will offer 3 medical continuation courses at the Center for Continuation Study in Minneapolis beginning in May, 1962: Ophthalmology for Specialists, May 7 through 9; Proctology for General Physicians, May 14 through 18; and Psychiatry for General Physicians, May 31 through June 2.

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THE INSTITUTE OF EXPERIMENTAL MEDICINE AND SURGERY, University of Montreal, requests help to rebuild a research library destroyed by fire. The Institute needs as many reprints of medical work as possible, especially those dealing with endocrinology and stress. The fire also destroyed publication mailing lists, and the Institute will be able to send reprints of its own publications only to readers who write to request them. Inquiries and literature should be mailed to Hans Selye, Professor and Director, Institute of Experimental Medicine and Surgery, University of Montreal, P. O. Box 6128, Montreal 26, Canada.

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THE UNIVERSITY OF MINNESOTA will take part in a cooperative project to examine the practicality of using electronic computers in diabetes research. The study will be directed by Dr. Arnold Lazarow, head of the anatomy department, and will be financed by a \$170,405 grant from the United States Public Health Service. If successful, the project may evolve computer techniques to retrieve information catalogued from diabetes-related literature, which now runs to about 2,500 articles yearly. The University's responsibility in the study will be to determine if computers could provide researchers with specialized information from literature related to a specific field. Other institutions in the project are Western Reserve University, Cleveland; the National Library of Medicine, Washington, D. C.; and the University of Rochester, New York.

North Dakota

DR. RAYMOND B. ALLEN, a native of Cathay, has been appointed chief of the Office of Research Coordination, an office of the World Health Organization which helps Latin American nations develop medical research programs. Dr. Allen most recently was director of the United States Economic Mission to Indonesia. He was dean of the College of Medicine of Wayne University, 1936-1939; executive dean of the Chicago professional schools at the University of Illinois and dean of the Medical School, 1939-1946; president of the University of Washington, 1946-1952; and chancellor of the University of California at Los Angeles, 1952-1959. Dr. Allen was Seattle's "First Citizen" in 1949.

• • • •

DR. MILTON O. BERG was elected president of the Kotana Medical Society, which includes all physicians from Tioga, Williston, Crosby, and Watford City. Dr. Berg is on the Tioga Community Hospital staff with Dr. James B. Hoyme.

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA,
NORTH DAKOTA, SOUTH DAKOTA, AND MONTANA

The Pathologist

ABOUT the turn of the century, pathology was the newest of the medical specialties. To a great extent, medicine was an exercise in diagnosis—and differential diagnosis at that. Without insulin, liver extract, the sulfas, and antibiotics, there was often little that could be done for the patient. Treatment too often was merely supportive and symptomatic. Surgical techniques were established but relatively limited in scope and area. Pathology, however, was a laboratory science and had an appeal to the student. It had the advantage, in his eyes, of being a more exact science, and the medical student looked up to the pathologist as the image to which he aspired. For example, Osler was originally drawn into pathology for this very reason.

In the decades from 1920 to 1950, the clinical sciences grew up. More and more was being done for the patient in the way of cure. Pernicious anemia was no longer pernicious. Radiology and roentgenology became increasingly important specialties. Surgery, with anesthesiology on the team, expanded into new fields. Thoracic surgery and neurosurgery filled dramatic roles. The medical student now tended to become enamored of these fields, relegating pathology, at times, to the status of an aid to the other clinical fields or to a specialty in necropsy.

Since 1950, there has been a tremendous growth of postgraduate education in residency programs. More and more the residents looked to pathology as an essential in understanding the basic process of disease; more and more often the pathologist served as a consultant, studying frozen sections and blood smears as a guide to the internist. The clinical laboratory burgeoned. The pathologist again came to be regarded as the image aspired to by medical students.

All through this period the pathologist was, in small and nonteaching hospitals particularly, the backbone of postgraduate education. It fell to him to "give answers." He organized the clinicopathologic conferences and often gave the definite opinion. His was the tissue committee responsibility—important not only in upgrading standards of practice but in staff teaching as well. Upon him fell the responsibility of the clinical laboratory. He was expected to be, and usually was, the student.

It is appropriate in this issue of THE JOURNAL-LANCET, dedicated to Dr. Leonard Larson, whose career is that of a small hospital pathologist, to point out the continuing important role of the pathologist, not only in the field of medical care but also in the field of medical education.

T. H. HARWOOD, M.D., *Guest Editor*
Dean and professor of clinical medicine
University of North Dakota School of Medicine

Interpretation of Liver Biopsy Without Clinical Data

ARCHIE H. BAGGENSTOSS, M.D.

Rochester, Minnesota

THE PRESENT STUDY was prompted by the question frequently asked by my clinical colleagues—namely, how accurate is the pathologist's interpretation of the histologic appearance of the liver when he does not have clinical data to help him? It is an intriguing question, and it occurred to me that, since the section of pathologic anatomy at the Mayo Clinic is not responsible for the pathologist's report on liver biopsies and is relatively isolated, geographically, from the patient and the attending physicians, it might be possible to obtain a definitive answer to the question by an independent study. Accordingly, it was arranged that duplicate sections of all liver biopsy specimens be sent to me unaccompanied by any clinical data. The experiment began in September 1958 and was terminated, after a review of 600 biopsies, in October 1961.

MATERIAL AND METHODS

The biopsy tissue was fixed in formalin and embedded in paraffin. Sections were cut 8 μ . in thickness and routinely stained with hematoxylin and eosin. Special stains for iron, amyloid, glycogen, and lipoids were utilized when indicated. Approximately 65 per cent of the biopsies were needle biopsies and about 35 per cent were wedge biopsies removed during the course of abdominal operations. Histologic sections were examined in detail and all changes involving parenchyma, portal tracts, ducts, and vessels were recorded, however minute these changes were. At the end of the report of the findings, a diagnosis was recorded whenever possible. When this was not possible, the designation "not diagnostic" was recorded. After the first 400 biopsy specimens were studied, those revealing neoplasms were no longer recorded because it was apparent that they offered no diagnostic difficulties except in determining the primary source of the metastatic neoplasm and in classi-

fying the primary hepatic neoplasm. The final 200 biopsy specimens were restricted, therefore, to nonneoplastic conditions.

The clinical, laboratory, and surgical records were reviewed about two months later and correlated with the histologic diagnosis. It was considered that within two months a definitive diagnosis would have been obtained by operative intervention, necropsy, or the subsequent course of the patient's illness. Even after this period, however, a number of cases remained in which the diagnosis was still indeterminate clinically. The cases in which the liver biopsy was termed "not diagnostic" included many of these instances of an indeterminate final clinical diagnosis. Many of the other cases in the "not diagnostic" category included those in which operative intervention had been carried out for conditions not involving the liver and in which, for various reasons, liver biopsy was performed. The surgical procedures included splenectomy, cholecystectomy, gastrectomy, colectomy, hysterectomy, and nephrectomy. Other conditions in which the liver biopsy was not diagnostic included illnesses involving fever of undetermined origin, anemia, and metastatic carcinoma in which the needle biopsy had missed the site of hepatic metastasis.

RESULTS

The final results of the study revealed 423 correct diagnoses (71 per cent), 128 instances in which the biopsy was not diagnostic (21 per cent), and 49 incorrect diagnoses (8 per cent). A further analysis of the correct and incorrect diagnoses by various diagnostic categories follows.

Carcinoma. Neoplasms in the first 400 cases included 118 cases of metastatic carcinoma, 9 of lymphoma, 4 of hepatoma, and 2 of cholangioma. These diagnoses were all proved correct by exploratory laparotomy, necropsy, or the subsequent course of the patient's illness.

Cirrhosis. A diagnosis of cirrhosis of the liver was made in 120 cases, and these likewise were

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TABLE 1
HISTOLOGIC DIAGNOSIS: CIRRHOSIS OF LIVER
(120 CASES)

<i>Cirrhosis</i>	<i>Cases</i>
Alcoholic	46
Laennec's	21
Postnecrotic	20
Obstructive	7
Posthepatitic	5
Unclassified	21

TABLE 2
HISTOLOGIC DIAGNOSIS: ERRORS IN CLASSIFICATION
OF CIRRHOSIS (8 CASES)

<i>Classification</i>		<i>Cases</i>
<i>Correct</i>	<i>Incorrect</i>	
Unclassified	Obstructive biliary	2
Posthepatitic	Obstructive biliary	1
Obstructive biliary	Postnecrotic	2
Posthepatitic	Laennec's	1
Toxic hepatitis with cirrhosis	Alcoholic	1
Unclassified	Focal	1

all proved correct by exploratory laparotomy, necropsy, or subsequent course. The types of cirrhosis encountered in 600 biopsies are shown in table 1, with the exception of pigmentary cirrhosis, which is considered separately. Although the diagnosis of cirrhosis always proved to be correct, errors in the classification of cirrhosis were made in 8 cases, and these are listed in table 2.

The criteria used in the diagnosis of cirrhosis and in the classification of the various types have been discussed in previous publications¹⁻⁴ and will not be repeated here. As can be seen from table 2, most of the difficulties centered around the differentiation of obstructive biliary cirrhosis from postnecrotic cirrhosis. Although several cases remained in the unclassified category because of insufficient data, the errors in classification were revealed by subsequent laparotomy, at which time obstruction of the bile ducts could be ruled out in 2 cases (considered obstructive biliary cirrhosis) and obstruction was discovered in 2 cases (called postnecrotic cirrhosis).

Pigmentary cirrhosis was observed in 25 cases. In all but 1 case, the diagnosis of hemochromatosis was correct; in the exception, the patient had hemolytic anemia with cirrhosis, and the diagnosis of hemochromatosis was not confirmed.

Chronic Alcoholism. A diagnosis of chronic alcoholism on the basis of the histologic changes

in the liver was made in 30 cases. Although such a diagnosis might seem unwarranted on a histologic basis, the interpretation proved to be correct in 22 cases (73 per cent) and incorrect in 8. The histologic criteria on which the diagnoses were based have been outlined previously⁵ and will not be repeated here. The 8 errors are listed in table 3. It is possible that the metabolic disarrangements occurring in cases of diabetes mellitus, malnutrition, and treatment with stilbestrol are responsible for histologic alterations in the hepatic parenchyma that resemble those produced in patients suffering from chronic alcoholism. The similar alterations in the 2 cases of Hodgkin's disease are unexplained, but the biopsies in both instances failed to reveal the characteristic granulomatous or lymphomatous lesions on which a diagnosis of Hodgkin's disease can be based.

Fatty Change of the Liver. This diagnosis was made in 12 cases. The associated clinical conditions presumably responsible for the histologic evidence were indeterminate in 7 cases, diabetes mellitus in 3 cases, and the malabsorption syndrome and obesity in 1 case each.

Hepatitis. A specific diagnosis of viral hepatitis was made histologically in 17 cases (table 4). The criteria used in this diagnosis have been outlined previously.⁶ The histologic diagnosis

TABLE 3
HISTOLOGIC DIAGNOSIS:
CHRONIC ALCOHOLISM (30 CASES)

<i>Diagnosis</i>	<i>Cases</i>	
	<i>Number</i>	<i>Per cent</i>
Correct	22	73
Incorrect	8	27
Condition proved to be:		
Diabetes mellitus	3	
Hodgkin's disease	2	
Malnutrition	1	
Stillbestrol treatment	1	
Viral hepatitis	1	

TABLE 4
HISTOLOGIC DIAGNOSIS: VIRAL HEPATITIS
(17 CASES)

<i>Diagnosis</i>	<i>Cases</i>
Correct	13*
Incorrect	4
Condition proved to be:	
Stricture of ducts	2
Carcinoma of ducts	1
Chronic ulcerative colitis	1

*Five with early cirrhosis

proved to be incorrect in 4 cases (24 per cent). The incorrect diagnoses involved 2 cases of stricture of the bile ducts and 1 case each of carcinoma of the common hepatic duct and chronic ulcerative colitis.

A diagnosis of hepatitis of indeterminate etiology was made in 11 cases. The various final diagnoses in these cases are listed in table 5. In no instance could the histologic diagnosis be proved wrong; in 2 instances it was the clinical impression that the process was viral. The 2 cases involving a clinical syndrome designated by the term primary biliary cirrhosis are interesting in this connection and will be discussed in the section on clinical diagnosis. In neither case, however, was there any evidence of cirrhosis as defined by the recognized histologic criteria.

The histologic diagnosis of granulomatous hepatitis was made in 13 cases. The final clinical diagnosis in these cases is shown in table 6. Apparently only 1 error was made and that was in a case in which the final diagnosis was lymphoma of the spleen. The possibility that the liver was coincidentally involved by a nonneoplastic granulomatous process must also be considered in this instance.

Extrahepatic Bile Duct Obstruction. This histologic diagnosis was made in 59 cases. It was

TABLE 5
HISTOLOGIC DIAGNOSIS: HEPATITIS (TYPE ?)
(11 CASES)

<i>Clinical diagnosis</i>	<i>Cases</i>
Primary biliary cirrhosis	2
Hepatitis (type ?)	2
Viral hepatitis	1
Chronic hepatitis	1
Serum hepatitis	1
Toxic hepatitis	1
Chronic ulcerative colitis	1
Hepatitis (?)	1
Indeterminate	1

TABLE 6
HISTOLOGIC DIAGNOSIS: GRANULOMATOUS
HEPATITIS (13 CASES)

<i>Clinical diagnosis</i>	<i>Cases</i>
Tuberculosis	3
Sarcoid	2
Fever, undetermined origin	2
Granulomatous hepatitis	2
Unclassified	2
Chronic hepatic disease	1
Lymphoma of spleen	1

TABLE 7
HISTOLOGIC DIAGNOSIS: OBSTRUCTION OF
EXTRAHEPATIC BILE DUCTS
(59 CASES)

<i>(Histologic diagnosis correct)</i> <i>Lesion</i>	<i>Cases</i>
Metastatic carcinoma	12
Stones	8
Carcinoma of ducts	4
Carcinoma of pancreas	3
Chronic pancreatitis	3
Stricture of ducts	2
Congenital biliary atresia	2
Polyp of common bile duct	1
Obstruction of duodenum	1
Not proved	1
<i>Total</i>	37 (63%)

TABLE 8
HISTOLOGIC DIAGNOSIS: OBSTRUCTION OF
EXTRAHEPATIC BILE DUCTS
(59 CASES)

<i>(Histologic diagnosis incorrect)</i> <i>Clinical diagnosis</i>	<i>Cases</i>
Primary biliary cirrhosis	5
Chronic ulcerative colitis	5
Chlorpromazine hypersensitivity	4
Cholangiolitic hepatitis	5
Chronic alcoholism	1
Serum hepatitis	1
Fever, undetermined origin	1
<i>Total</i>	22 (37%)

correct in 37 cases (63 per cent) and incorrect in 22 cases (37 per cent). The lesions responsible for the obstruction of the ducts are indicated in table 7. The final clinical diagnosis in the cases incorrectly diagnosed as extrahepatic duct obstruction is listed in table 8. In none of the cases in which the clinical syndrome of primary biliary cirrhosis was present was there histologic evidence of cirrhosis of the liver by generally accepted histologic criteria.

Intrahepatic Cholestasis. When the predominant histologic change was bile stasis without the usual changes associated with either hepatitis or extrahepatic bile duct obstruction, a histologic diagnosis of intrahepatic cholestasis was made. This diagnosis was made in 9 cases. The final clinical diagnoses are listed in table 9. As can be seen from the table, the histologic diagnosis was probably correct as far as it went in all but the single case of a metastatic lesion. Material from the metastatic lesion had not been obtained in the biopsy; the bile stasis was prob-

TABLE 9
HISTOLOGIC DIAGNOSIS: INTRAHEPATIC
CHOLESTASIS (9 CASES)

<i>Clinical diagnosis</i>	<i>Cases</i>
Primary biliary cirrhosis	4
Chronic ulcerative colitis	2
Cholangiolitic hepatitis	1
Rheumatoid arthritis and L.E.	1
Metastatic carcinoma of liver	1

TABLE 10
CLINICAL DIAGNOSIS: OBSTRUCTION OF
EXTRAHEPATIC BILE DUCT
(41 CASES)

<i>Histologic diagnosis</i>	<i>Cases</i>
Correct	37
Incorrect	4
Condition was called:	
Viral hepatitis	3
Peliosis hepatitis	1

ably the result of obstruction of the intrahepatic bile ducts. Ordinarily, in these cases the histologic appearance is the same as in obstruction of the extrahepatic bile ducts.

CLINICAL DIAGNOSES

Up to this point I have listed the results of the histologic diagnoses in terms of the correct and final diagnosis made by surgical exploration, other laboratory studies, necropsy examination, or subsequent course of the disease. In analyzing the results of this study it is also helpful to consider the final clinical or necropsy diagnosis in various accepted categories and then to compare these with the histologic diagnoses.

Thus, the final clinical diagnosis was extrahepatic bile duct obstruction in 41 cases. The correct histologic diagnosis by biopsy was made in 37 of these cases (90 per cent), and an incorrect diagnosis was made in 4 cases, as listed in table 10. The percentage of correct diagnoses in this group was even higher than could be predicted from a previous study,⁷ in which the histologic criteria for a diagnosis of extrahepatic bile duct obstruction were outlined.

The clinical syndrome of primary biliary cirrhosis was present in 12 cases. The correct histologic diagnosis in terms excluding extrahepatic bile duct obstruction was made in only 7 cases (58 per cent). An incorrect diagnosis was made in 5 cases (42 per cent), and in each instance the condition incorrectly cited was extrahepatic bile duct obstruction (table 11).

Even more disappointing results were obtained

in the clinical syndrome of cholangiolitic hepatitis. In 5 of 6 cases the histologic diagnosis was extrahepatic bile duct obstruction. The same disappointing results were obtained in 4 cases of chlorpromazine (Thorazine) hypersensitivity with jaundice. In each instance the histologic diagnosis was extrahepatic bile duct obstruction (table 12).

The clinical diagnosis of chronic ulcerative colitis was made in 17 cases. The correct histologic diagnosis in terms excluding extrahepatic bile duct obstruction was made in 8 cases (47 per cent), and the incorrect diagnosis of extrahepatic bile duct obstruction was made in 5 cases (29 per cent). In the remaining 4 cases (24 per cent) the biopsy was not diagnostic (table 13); in 3 of these 4 no jaundice was present at the time of the biopsy.

COMMENT

It is apparent from this study that even in the absence of clinical data the histologic diagnosis of neoplastic disease or cirrhosis of the liver is almost always accurate. The precise classification of the variety of cirrhosis encountered offers

TABLE 11
CLINICAL DIAGNOSIS: PRIMARY BILIARY CIRRHOSIS
(12 CASES)

<i>Histologic diagnosis</i>	<i>Cases</i>
Correct	7
Intrahepatic cholestasis	4
Hepatitis (type ?)	2
Early cirrhosis	1
Incorrect	5
Condition was called:	
Obstruction, extrahepatic bile ducts	

TABLE 12
CLINICAL DIAGNOSIS: (1) CHOLANGIOLITIC HEPATITIS
(6 CASES) AND (2) CHLORPROMAZINE
HYPERSENSITIVITY (4 CASES)

<i>Histologic diagnosis</i>	<i>Cases</i>
(1) Cholangiolitic hepatitis	(6)
Correct	1
Intrahepatic cholestasis	
Incorrect	5
Condition was called:	
Obstruction, extrahepatic bile ducts	
(2) Chlorpromazine hypersensitivity	(4)
Incorrect	4
Condition was called:	
Obstruction, extrahepatic bile ducts	

some difficulties, but these are generally resolved with the help of the clinical data, for example, in distinction of obstructive biliary cirrhosis from postnecrotic cirrhosis. In a broad sense, the morphologic diagnosis of postnecrotic cirrhosis may be correct even if the causative factor is obstruction of the biliary tree, since, by definition, postnecrotic cirrhosis embodies all cases in which the zones of collapse or the fibrous scars on microscopic examination include 3 or more portal triads abnormally aggregated at 1 or more places in the histologic section.⁸

In the histologic diagnosis of chronic alcoholism, the errors can likewise be readily corrected by clinical data in most instances.

In the diagnosis of viral hepatitis, one error could not have been corrected without an exploratory laparotomy. In the 2 cases of stricture of the bile ducts and in the single case of chronic ulcerative colitis, the clinical data would have been helpful in arriving at a correct diagnosis. If one combines all the cases of hepatitis, exclusive of the granulomatous variety, the histologic diagnosis in this series was correct in 86 per cent of the cases even without knowledge of clinical data.

The greatest difficulty in this study, as in the experience of many other pathologists, was encountered in the differentiation of extrahepatic bile duct obstruction from other conditions that cause intrahepatic cholestasis. It is apparent from this study that, if extrahepatic bile duct obstruction did in fact exist, the correct histologic diagnosis was almost always made. The exact figures were 37 of 41 cases, or 90 per cent (table 10). The difficulty arose, however, from the overdiagnosis of this condition from the histologic appearance of the liver. Thus, 5 of 12 cases of primary biliary cirrhosis, 5 of 6 cases of cholangiolitic hepatitis, all 4 cases of chlorpromazine hypersensitivity, and 5 of 17 cases of

chronic ulcerative colitis were incorrectly diagnosed as extrahepatic bile duct obstruction on a histologic basis. It is, of course, apparent that the liver biopsies in the cases of chlorpromazine hypersensitivity and chronic ulcerative colitis could have been correctly interpreted with the help of the clinical data. It is interesting in this regard that the cases of chlorpromazine hypersensitivity revealed the hepatic changes that are regarded as characteristic of extrahepatic bile duct obstruction rather than those of toxic hepatitis. However, in the cases of primary biliary cirrhosis and cholangiolitic hepatitis, the clinical data are often as misleading as the histologic findings, and little help can be expected by the pathologist from such data. It is obvious that histologic criteria for making the differentiation, at least in the hands of this investigator, are inadequate; either new criteria must be sought or some other test devised for making the differentiation. At the present time, it appears that surgical exploration of the bile ducts is still necessary in order to make an accurate differentiation in some cases.

SUMMARY AND CONCLUSIONS

Six hundred liver biopsies were reviewed without reference to any clinical information in order to evaluate the adequacy of histologic changes for accurate diagnosis. The histologic diagnosis was correct in 423 cases (71 per cent), not diagnostic in 128 (21 per cent), and incorrect in 49 (8 per cent). If one excludes the cases in which the biopsy was not diagnostic, 89 per cent of diagnoses were correct and 11 per cent incorrect.

The presence of neoplastic disease or cirrhosis of the liver presented no difficulties in arriving at a correct diagnosis. Somewhat greater difficulty was encountered in the diagnosis of chronic alcoholism and hepatitis, but accuracy was obtained in 73 and 86 per cent of the cases, respectively.

The greatest difficulty was encountered in correctly differentiating cases with extrahepatic bile duct obstruction from those in which the cause of the jaundice was intrahepatic. Thus, although a histologic diagnosis of extrahepatic bile duct obstruction was made in 59 cases, this diagnosis was correct in only 37 cases (62 per cent). Most of the errors were in cases clinically designated as primary biliary cirrhosis (5 cases), chronic ulcerative colitis (5 cases), chlorpromazine hypersensitivity (4 cases), and cholangiolitic hepatitis (5 cases).

The histologic diagnosis of intrahepatic cholestasis, on the other hand, was made in 9 cases and was correct in 8. It was apparent that extra-

TABLE 13
CLINICAL DIAGNOSIS: CHRONIC ULCERATIVE
COLITIS (17 CASES)

<i>Histologic diagnosis</i>	<i>Cases</i>
Correct	8
Intrahepatic cholestasis	3
Cholangiolitic hepatitis	2
Laennec's cirrhosis	2
Hepatitis (type ?)	1
Incorrect	
(Called extrahepatic obstruction)	5
Not diagnostic	4 ^a

^aThree without icterus

hepatic bile duct obstruction was overdiagnosed and that intrahepatic cholestasis was underdiagnosed.

When the cases are analyzed from the viewpoint of the final clinical diagnoses, 37 of 41 cases (90 per cent) of extrahepatic bile duct obstruction were correctly diagnosed histologically. Primary biliary cirrhosis, on the other hand, was correctly diagnosed histologically in only a little more than half the cases. In regard to cholangiolitic hepatitis, the results were even worse, since 5 of 6 cases were incorrectly diagnosed. All 4 cases of chlorpromazine hypersensitivity were incorrectly diagnosed as extrahepatic bile duct obstruction. In the cases of chronic ulcerative colitis, 8 diagnoses were correct in terms of excluding extrahepatic bile duct obstruction, 5 were incorrect, and 4 were not diagnostic. In regard to both chlorpromazine hypersensitivity and chronic ulcerative colitis, the clinical data would have been helpful in arriving at a correct histologic diagnosis. In regard to the clinical syndrome of primary biliary cirrhosis and cholangiolitic hepatitis, however, it is doubtful that clinical data would have been of any help.

It seems apparent that the liver reacts in a similar manner to a wide variety of injuries. Therefore, if unnecessary surgical exploration is to be avoided, either revision of the present histologic criteria or the elaboration of new tests is needed to permit the differentiation of some of the clinical entities.

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RETICULOCYTOSIS and nucleated red cells in the peripheral blood of patients with congestive heart failure suggest an unfavorable prognosis. The reticulocyte count appears to be a more useful prognostic tool than the nucleated red cell count. Among 15 patients with severe congestive heart failure, the reticulocyte count was more than 3 per cent in all of 5 patients who died and less than 2.2 per cent in all of 10 survivors. Nucleated red cells were found in the peripheral blood of 2 of the patients who died and none of those who survived. Arterial oxygen saturation was reduced in all except 1 of the 15 patients. Good correlation was noted between reticulocytosis and degree of hypoxemia.

J. THOMAS, O. MICHAEL, and C. W. EWELL: Reticulocytosis and hypoxemia as prognostic signs in congestive heart failure. *Circulation* 24:1151-1153, 1961.

Inhibition of L.E. Phenomenon by EDTA

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SINCE THE RECOGNITION of the lupus erythematosus cell by Hargraves and associates¹ in 1948 and the subsequent development of techniques for demonstration of L.E. phenomenon,² observations have been made on the factors, both inhibitory and productive, which influence the phenomenon.³⁻⁶

Several authors have shown changes due to anticoagulants.⁴⁻⁶ In general, one may say that inhibition of the coagulation phenomenon usually inhibits the L.E. phenomenon. Marrow has been shown to be an excellent source of both damaged and viable cells as a substrate for the action of the L.E. plasma or serum.⁷ In marrow preparations, in order to make a thorough study for blood dyscrasias, one needs adequate material and a means of anticoagulation to facilitate the preparations of buffy coat smears, sections, and so forth.⁸ The anticoagulant of choice has been shown by many authors to be dry heparin,⁸ which was used routinely in the preparation of the marrows in this laboratory until it was noted that staining was very poor (acid) on many of the heparinized specimens. The sodium salt of ethylenediaminetetraacetate (EDTA) was substituted with good results; the staining was apparently not altered by the anticoagulant.

In two recent marrow studies, hematoxylin-body formation occurred without phagocytosis by the neutrophils. In both cases a marrow sample was collected, first-drop smears were prepared, and the remaining marrow was placed in a paraffin-lined tube containing 1 or 2 drops of 10 per cent sodium EDTA. The marrow containing anticoagulant was used in preparing buffy coat smears, particle smears, and paraffin sections.

CASE REPORTS

Case 1. On examination of the first-drop smears, no evidence of L.E. phenomenon was seen, as one would expect with no incubation of the specimen. Buffy coat and particle smears contained many L.E. hematoxylin bodies (figure 1);

however, none of these appeared to be phagocytosed by the neutrophils in the smears. Hematoxylin bodies were reported in the specimen, and an L.E. clot test⁹ was requested. This test was performed on the following day with positive results.^{3,6} The test was repeated on the third day and also showed positive results (figures 2 and 3).

Case 2. The marrow was prepared in the same manner as in case 1. The first-drop smears

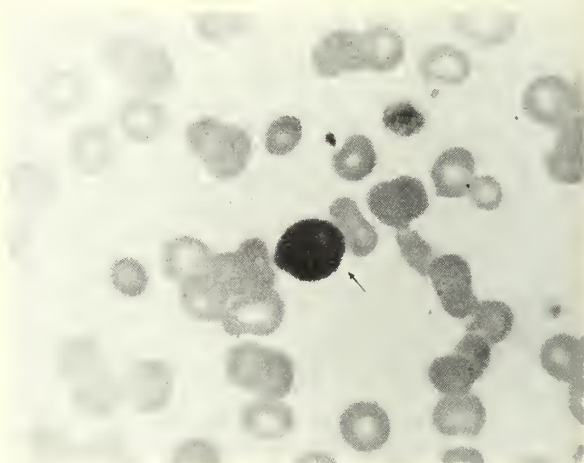


Fig. 1. Hematoxylin body from case 1. Marrow buffy coat

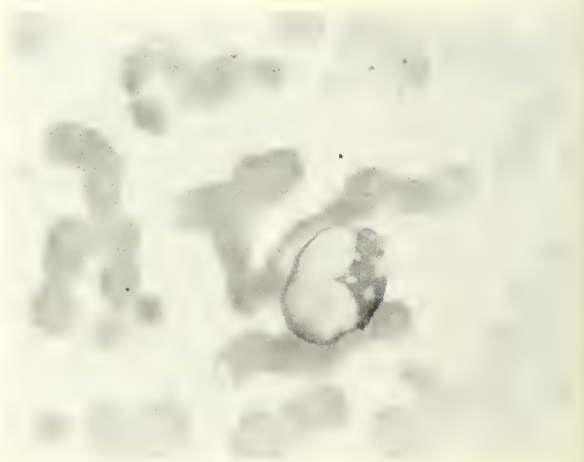


Fig. 2. L.E. cell from case 1. Clot test

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showed no evidence of L.E. phenomenon. The buffy coat in this case contained many hematoxylin bodies (figure 4), none of which appeared to be phagocytosed by the neutrophils. When the hematoxylin bodies failed to be phagocytosed in the first smears made from the buffy coat at thirty minutes, incubation of the plasma and buffy coat mixture was continued, with smears prepared at thirty-minute intervals for two hours. At the end of this time staining of the marrow cells was still very good, but the phagocytosis had not appeared. Smears made from the mixture at twelve hours also showed no phagocytosis of hematoxylin bodies. A subsequent clot test performed on the following day showed positive results (figures 5 and 6).

On the third day, 10 ml. of peripheral blood was taken from this second patient by venipuncture; 5 ml. was allowed to clot in the procedure for the usual L.E. clot test, and 5 ml. was placed in a tube with 1 drop of 10 per cent EDTA solu-

tion. At the end of two hours, smears were prepared from both buffy coats (sieved clot and the EDTA buffy coat). Smears from the clot test were positive as before, while smears from the EDTA buffy coat showed no evidence of L.E. phenomenon, no hematoxylin bodies or phagocytosis.

SUMMARY

In this report, 2 cases are reviewed in which L.E. patients gave negative L.E. tests when EDTA was used in the marrow specimens. This was due to inhibition of phagocytosis of hematoxylin bodies by the neutrophils. EDTA effect on the peripheral blood was studied in 1 case, showing inhibition of hematoxylin-body formation as well.

Note. We have now changed our marrow procedure to include the preparation of a small portion of clotted marrow. As before, the remaining marrow is placed in a tube with EDTA and the

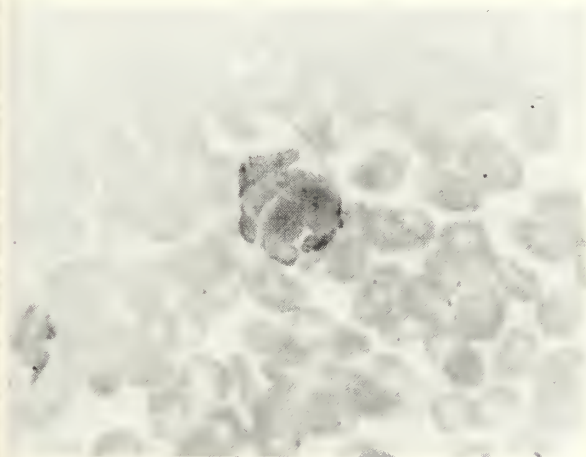


Fig. 3. L.E. cell from case 1. Clot test

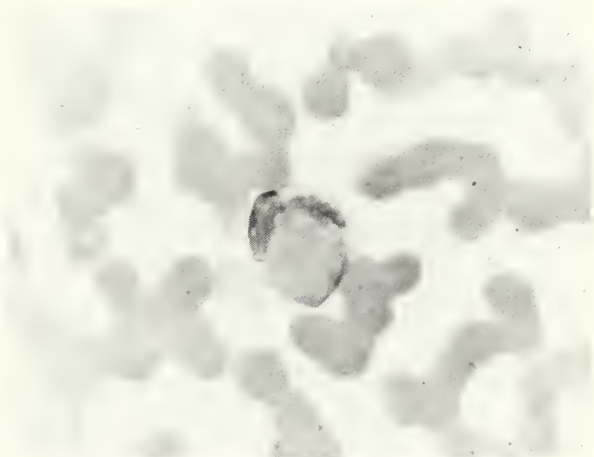


Fig. 5. L.E. cell from case 2. Clot test

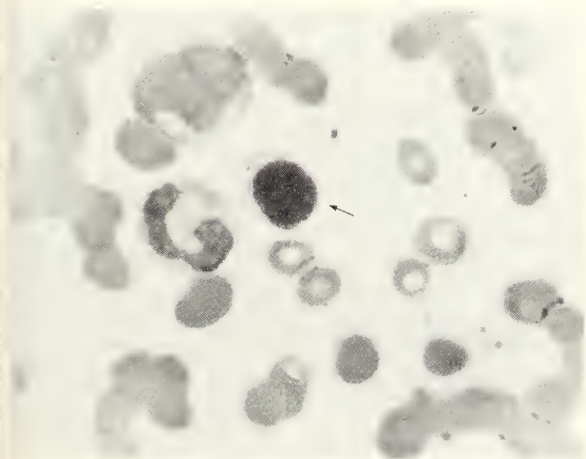


Fig. 4. Hematoxylin body from case 2.
Marrow buffy coat

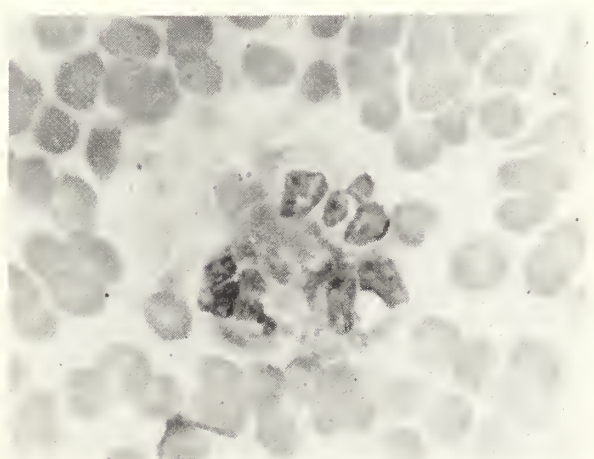


Fig. 6. L.E. cell from case 2. Rosette

buffy coat smears, particle smears, and sections are prepared from it. The clotted marrow is mashed, and smears are made for the study of L.E. phenomenon.

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EFFECTIVENESS of corticosteroid treatment in patients with nephrotic syndrome resulting from primary renal disease can be predicted fairly accurately on the basis of glomerular changes in percutaneous renal biopsy specimens. Examination of the specimens with the light microscope reveals 4 types of glomerulonephritis—membranous, proliferative, membranous and proliferative combined, and sclerosing—and glomeruli without change or with slight changes not uniform or general enough to permit classification. In patients with no or slight glomerular changes but undisturbed renal function or with proliferative glomerulonephritis, steroid treatment usually results in complete loss of edema, proteinuria, hypercholesteremia, and hypoalbuminemia as well as improvement in the appearance of the glomeruli. In most patients with membranous or combined membranous and proliferative glomerulonephritis, treatment produces either diuresis with decrease in proteinuria, hypercholesteremia, and hypoalbuminemia or no effect at all. Treatment usually is ineffective in patients with sclerosing renal lesions.

Administration of prednisone (Meticorten) to 19 patients with nephrotic syndrome caused by primary renal disease resulted in complete remission in 1 of 6 with membranous, 3 of 4 with proliferative, none of 3 with combined membranous and proliferative, none of 2 with sclerosing, and 3 of 4 with slight or no glomerular changes. Treatment was ineffective in 4 of the patients, each with a different kind of glomerulonephritis.

R. R. BURCH, M. A. PEARL, and W. H. STERNBERG: A clinicopathological study of the nephrotic syndrome. *Ann. Int. Med.* 56:54-67, 1962.

By Sight or Cytology?

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EXFOLIATIVE CYTOLOGY as a screening test for carcinoma of the cervix has been used by our department since March 1952. From that time through December 1960, we processed 13,037 smears, 3,878 of which were from pregnant patients. The exact number of patients involved is not known, since many have had repeat studies. In all, there were 234 patients in whom the initial cytology was interpreted as class III, IV, or V. If patients with known cancer and those with glandular cell atypia are omitted, there remain 190 with sufficient squamous cell abnormalities to place their cytology in the suspicious or positive classes (table 1). Subsequent discussion is related to this group of 190 patients.

METHODS AND MATERIALS

Smears were taken as cervical scrapings and fixed in ether-alcohol or alcohol solutions. Staining was as recommended by Papanicolaou. Since 1958, a cytotechnician has performed the initial screening; final evaluation has been made by the author. Biopsy material was evaluated by the Department of Pathology at the University of North Dakota Medical School. Whenever questions arose regarding either the smears or sections, additional opinions were obtained.

A repeat smear and a 4-quadrant biopsy were requested for patients with class III cytology. In those with classes IV and V, a repeat smear with cold-knife conization and curettage was suggested.

RESULTS

Class III smears. There were 124 patients in this group, twelve of whom were pregnant. Of the 124, 57 had cervical biopsies (table 2). Chronic cervicitis was reported in 52, atypical epithelium in 2, and in situ squamous cell carcinoma in the remaining 3.

In the 54 patients with initially benign lesions,

3 had subsequent biopsies and 6, hysterectomy. In all of these, the cervixes were benign. Two others were treated by cautery. Twenty-three had one or more negative smears and 20 were not followed further.

None of the in situ lesions was suspected; 1 cervix was considered normal, and the other 2 had erosions. These patients were treated by total abdominal hysterectomy, and none was found to have residual tumor. One lesion was diagnosed on the basis of 4-quadrant biopsy material. Another of the 3 patients was in early pregnancy at the time of the class III cytology report. A cold-knife cone biopsy confirmed the suspicious cytology, and an immediate abdominal hysterectomy was performed.

Of the 124 patients, 3 others had hysterectomies without preceding cervical biopsy. The cervixes of these revealed chronic cervicitis.

Repeat cytology only was done in 44 patients; in 6, follow-up smears were read as class III. Subsequently, 2 of these became negative, and the other 4 were not followed further. In 7, oral estrogens restored atrophic changes to a normal functional cytology. Another patient was found to have a repeat class V cytology. She died, without biopsy, of metastasis from cervical carcinoma. Of the total patients in this group, 19 were not followed at all, only 2 of whom were among the obstetric group.

The 1 remaining patient had previously undergone a Manchester procedure for prolapse, which included cervical amputation. She became pregnant following this, and a class III cytology was obtained which subsequently became negative.

Class IV smears. There were 35 patients in this group, 7 of whom were pregnant. Of the 35,

TABLE 1

Interpretation	Pregnant	Non-pregnant	Total
Class III	12	112	124
Class IV	7	28	35
Class V	3	28	31
Totals	22	168	190

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TABLE 2

Class III	Number of patients	Chronic cervicitis	Atypical epithelium	In situ carcinoma
4-quadrant biopsy	34	31	2	1
Cone biopsy	23	21	0	2
Totals	57	52	2	3

TABLE 3

Class IV	Clinically suspected	Clinically unsuspected		
		No comment	Cervix normal	Erosion, etc.
Benign		5	11	8
In situ carcinoma		3	3	3
Invasive carcinoma	1			1

26 had cervical biopsies. In 10 instances the initial biopsy was positive for squamous cell carcinoma; 8 of these were in situ lesions and 2 invasive. Only 1 of the 10 patients was pregnant.

Of the 14 patients with chronic cervicitis on initial biopsy, 4 were biopsied a second time because of persistently abnormal cytology. The results were 1 (three months post partum) with cervical carcinoma in situ, 1 with atypical epithelium, and 2 with chronic cervicitis. Another 5 patients had 16 class I or III follow-up smears but no further biopsy. The remaining 5 were lost to follow-up. The 2 patients with atypical epithelium on initial biopsy had repeat smears, all of which were negative.

Of the 9 patients not having biopsy, 5 had follow-up smears only. Another 2 had no further studies, and 1 was treated by hysterectomy for other reasons. The final patient had an ulcer of the vaginal vault which was benign on biopsy.

Thus, a total of 9 in situ and 2 invasive lesions were discovered in this group of 35 patients. Only 1 of these was suspected (table 3).

All 11 patients were treated. Conventional radiation therapy was given those with invasive carcinoma. Table 4 lists the types of therapy in the 9 patients with in situ lesions. Of those not having hysterectomy, 1 received definitive therapy based on material present in a 4-quadrant biopsy. No tumor was found in the removed cervical stump. The second patient, 23 years of age and pregnant when a class IV smear was obtained, was treated by conization. During this pregnancy, 4-quadrant biopsy revealed chronic cervicitis with erosion. Postpartum follow-up smears at six weeks and three months were read as class IV. A wide cervical cone biopsy speci-

men at thirteen weeks postpartum contained an in situ squamous cell carcinoma. Subsequent cytology has remained negative. Two of the other patients had residual tumor in the hysterectomy specimen.

Class V smears. All 31 patients with initial smears read as class V received cervical biopsies (table 5). Three were pregnant. In the 8 with 4-quadrant and the 23 with cone biopsies, 21 were positive for squamous cell carcinoma of the cervix. No patient had cone biopsy during pregnancy.

Of the 8 patients with 4-quadrant biopsies, 3 were pregnant. Of the latter, 1 had an in situ cervical carcinoma. Her cytology studies have been repeatedly normal since delivery. Therefore, the lesion should be suspect as having been overread, regressed, or removed by the biopsy procedure. Invasive lesions were found in 2 of the 5 nonpregnant patients.

Of the 23 patients having initial cone biopsies, 18 were positive for carcinoma—5 for invasive and 13 for in situ lesions.

In the remaining 10 patients, 3 biopsies demonstrated "atypical basal cell hyperplasia." Of the 10, 2 were pregnant when biopsied. Follow-up on these 2 led to subsequently negative smears and/or biopsies.

In the other 7 patients whose first biopsies were read as "chronic cervicitis," 1 had repeat biopsy which revealed invasive squamous cell carcinoma. A second patient underwent an abdominal hysterectomy for other reasons, and the removed cervix contained an in situ cervical lesion. A third had a cone biopsy after the 4-quadrant procedure was negative; this also revealed an in situ lesion. Two additional patients had subsequent negative cytologic studies, and the remaining 2 were lost to follow-up.

TABLE 4

Procedure	CLASS IV	
	Residual tumor	No residual tumor
Abdominal hysterectomy	2	4
Vaginal hysterectomy		1
Conization or cervicectomy		2

TABLE 5

Class V	Number of patients	Chronic cervicitis	Atypical epithelium	In situ carcinoma	Invasive carcinoma
4-quadrant biopsy	8	4	1	1	2
Cone biopsy	23	3	2	13	5
Totals	31	7	3	14	7

In summary, 1 additional invasive and 2 in situ lesions were added, making a total of 16 in situ and 8 invasive squamous cell cervical carcinomas in this group of 31 patients.

Four invasive carcinomas were clinically suspected and 4 others were not (table 6). In 1 of the latter, no comment was made on the record regarding the appearance of the cervix. All 16 in situ lesions were unsuspected. The cervix was described as being abnormal, however, in 8. There were then 20 unsuspected lesions—16 in situ and 4 invasive—discovered by exfoliative cytology.

The 8 invasive lesions were treated by conventional radiation methods, while 13 of the patients with in situ lesions were treated by hysterectomy, 6 having residual tumor in the removed specimen (table 7). Another patient was treated by radiation, and 2 more had follow-up smears or biopsies only.

False-negative smears. In this study 2 patients were discovered as having "false-negative" cytology. Both were pregnant when the diagnosis was made. The first exhibited a prolapsed, degenerating fibroid and antepartum hemorrhage. On biopsy, the lesion was found to be an invasive polypoid squamous cell cervical carcinoma. Negative cytologic tests, all obtained during pregnancies, had been reported three years, one year, and five months previous to biopsy. One month following biopsy, before radiation treatment was begun, a class III smear was obtained.

The second patient's first smear was read as class I and was secured during the fourth month of a previous pregnancy. Five months following delivery of this child, the patient was again

TABLE 6

Class V	Clinically suspected	Clinically unsuspected		
		No comment	Normal cervix	Erosion, etc.
In situ carcinoma		5	3	8
Invasive carcinoma	4	1	3	
Totals	4	6	6	8

TABLE 7

Class V	Number of patients	No residual tumor	Residual tumor
Abdominal hysterectomy	11	7	4
Vaginal hysterectomy	2		2
Radiation	1		
Smears only	2		

TABLE 8

Summary	Class III	Class IV	Class V	False Negative	Totals
Nonpregnant					
Invasive carcinoma		2	8		10
In situ carcinoma	2	8	15		25
Pregnant					
Invasive carcinoma				1	1
In situ carcinoma	1	1	1	1	4
Total carcinoma	3	11	24	2	40
Total patients	124	35	31	2	192

found to be pregnant. During this examination, the cervix exhibited several areas of leukoplakia about the external os. A cervical smear and 4-quadrant biopsy were done. The smear was interpreted as class I, and the biopsies reported "leukoplakia of the cervix with nuclear atypism." Further evaluation of the original sections led to the diagnosis of "squamous cell carcinoma of the cervix" with "questionable early invasion." The smear was then restained, restudied, and referred elsewhere for evaluation, with the final interpretation being class V.

A month after the original biopsy, a repeat 4-quadrant biopsy revealed only cervical erosion with epidermidization. Repeat cytologic studies each month during pregnancy and at six weeks post partum remained class V. A 4-quadrant biopsy at six weeks post partum was positive for preinvasive squamous cell carcinoma of the cervix with extensive glandular extension. This was confirmed by subsequent cone biopsy. No residual tumor was found in the hysterectomy specimen. This is the only patient with a positive diagnosis of cancer in the original survey of 2,000 pregnant patients.

DISCUSSION

In the 190 patients with suspicious or positive cytology, 38 squamous cell cervical carcinomas were found, a yield of only 20 per cent (table 8). This yield rate increased with the abnormality of the cytology (2.3 per cent for class III, 31.4 per cent for class IV, and 74.1 per cent for class V). These figures are one indication that we have leaned toward the side of "overreading" our material, but they also reflect the fact that our follow-up has not been ideal.

Referring again to table 8, if the 2 patients with false-negative smears are included, 40 cervical squamous cell lesions were found in a total of 192 patients. Of these, 11 were invasive, 1 of

TABLE 9

Summary	Invasive carcinoma	In situ carcinoma	Totals
Clinically suspected	5(1)		6
Clinically unsuspected			
No comment	1	8	9
Cervix Normal	3	6(1)	10
Cervix eroded, etc.	1	11(3)	15
Totals	11	29	40

Numbers in parenthesis indicate pregnant patients.

which was in a pregnant patient. In situ lesions were found in 29 patients, 4 of whom were pregnant. The average ages were 52.5 years for patients with invasive lesions, 42.4 years for those with in situ lesions, and 29 years for the pregnant patients.

In 6 instances, all in cases of invasive cancers, notations on the records were of such a nature as to indicate that the physician was suspicious of malignancy (table 9). The other 5 invasive tumors were unsuspected, and no in situ lesion was suspected. This would indicate either that our staff relies a great deal on the cytologic method for detection or that they have a very high threshold of suspicion for cervical cancer. We feel the former is warranted, since in 84 per cent of incidences (32 out of 38 cases) the staff was alerted by the cytologic study. The method failed them only twice in the seven years and ten months covered in this study. Conversely, in the same period of time, *sight* proved of value in only 1 more than half the invasive lesions found. Furthermore, excepting the 2 patients with false negative cytology, no patient with carcinoma of the cervix was diagnosed by our staff during this time without having abnormal exfoliative cytology.

Both failures were in pregnant patients. In the first case, the lesion was not discovered until it became gross and produced antepartum bleeding. All of the previous class I smears from this patient have been reviewed and sent elsewhere for opinion; none has been found to contain abnormal cells, thus representing a failure of the method. In the second instance, biopsy at the time of the smear was also first interpreted as atypical but benign. Further study and additional opinions led to the correct diagnosis. Re-examination of the smear revealed that it was completely misinterpreted. This represents a laboratory error.

Some comment is in order regarding false-positive smears. Previous reference has been

made to our low percentage of proved lesions compared with the total number of abnormal cytologic studies. For the benefit of the patient, we would rather err in this direction than in the opposite one. It may be difficult to be absolute in our evaluation over a short interval of time. We cannot predict what will be found much later in patients having a so-called false-positive smear at any one time. To illustrate, we now have a patient from whom a class III smear was obtained in 1957. In 1961, with no follow-up in the interval, she had a class IV smear and still refused biopsy.

All but 2 of the in situ lesions received treatment based on findings from cold-knife cone biopsy material (table 10). In neither case was residual tumor found in the removed specimen. Nevertheless, unless invasive carcinoma is found, we do not believe that one is justified in instituting definitive therapy on the basis of punch biopsy material alone.

In 7 of the 8 patients with in situ lesions, the residual focus was minimal or completely excised. The 1 exception illustrates a problem which plagues the operating physician. The patient was 1 of the 6 with in situ carcinoma discovered during the Grand Forks District Medical Society Survey of 1,001 women. Her initial smear was interpreted as being class IV. Biopsy using the 4-quadrant procedure yielded inadequate material. Repeat smears were classes III and V, and cone biopsy showed an equivocal lesion. The total abdominal hysterectomy specimen contained a tiny focus of an in situ carcinoma within the endocervical canal, but a larger area of in situ carcinoma was found in the removed vaginal cuff. A Schiller test to the cervix and vault was not done preoperatively. Such a test may have better demarcated the lesion for biopsy. Subsequent smears from the vaginal vault have been negative.

In two instances of in situ carcinoma, we believe the treatment employed, although adequate to destroy the lesion, was more radical

TABLE 10

Treatment of in situ lesions	Number of patients	No residual tumor	Residual tumor
Abdominal hysterectomy	21	15	6
Vaginal hysterectomy	3	1	2
Cervicectomy	2	2	
Radiation	1		
Follow-up smears or biopsy	2		
Totals	29	18	8

than indicated. The first patient was a young woman given radium and external radiation, and the second was subjected to abdominal hysterectomy in the presence of a known early pregnancy.

SUMMARY

A review of 13,037 cervical cytologic smears has been presented, among which 190 patients, 22 of whom were pregnant, were found to have suspicious or positive squamous cell abnormalities. Of this group, 38 patients were proved to have 10 invasive and 28 in situ squamous cell cervical carcinomas. An additional 2 patients were found to have cervical carcinomas and false-negative cytology. Of the 40 patients with carcinoma, 5 were pregnant.

Clinical impressions relying on *sight* and *palpation* roused suspicion in the minds of attending physicians only six times. Discovery of the remainder of the lesions depended upon the alerting influences of *cytology*.

Supported in part by 2 grants from the North Dakota Division of the American Cancer Society. The first allowed the survey of 2,000 pregnant women at the time of their initial prenatal examination. The purpose of the second was to stimulate interest in routine cytology among the members of the Grand Forks District Medical Society. The latter was carried out simultaneously with an extensive public education program. A total of 1,001 women were surveyed in this project.

We wish to thank Drs. R. R. Greene and Leon A. Carrow of the Department of Gynecology, Northwestern University Medical School, Chicago, for their aid as consultants for the histologic sections and cytologic smears.

ABERRATIONS in depolarization, repolarization, or both of premature ventricular beats on electrocardiograms suggest myocardial disease. Evidence of premature ventricular beats was found in 411 of 4,000 hospitalized subjects. The pattern was abnormal in 242, all with evidence of myocardial disease; 224 of these had other electrocardiographic signs of myocardial disease. The commonest abnormality was of depolarization, repolarization, or both, but the pattern of acute myocardial infarction was found in 13 patients and the duration of the QRS complex was longer than 0.18 second in 7.

1007, 1961.

L. A. SOLOFF: Ventricular premature beats diagnostic of myocardial disease. *Am. J. M. Sc.* 212:315-319, 1961.

RESPONSE of coronary blood flow to intravenous nicotine administration is impaired in dogs with coronary artery ligation or narrowing. The more coronary flow is impaired, the more extreme is the relative coronary insufficiency produced by nicotine. In dogs with occlusion of the anterior descending branch of the coronary artery, base-line blood flow is diminished and that after nicotine injection is augmented less than in controls. In animals with constriction of both main branches of the left coronary artery produced by casein rings, augmentation of response to nicotine is reduced even more. During nicotine administration, coronary vascular resistance and myocardial use of oxygen decrease. Effect on blood flow is similar to that observed in anoxemia with coronary insufficiency. Such findings appear relevant to possible effects of nicotine in human beings with coronary artery disease.

S. BELLET, J. W. WEST, O. F. MÜLLER, and U. C. MANZOLI: Effect of nicotine on the coronary blood flow and related circulatory parameters. *Circulation Res.* 10:27-31, 1962.

Repeated Paradoxical Embolism

Report of a Case

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PARADOXIC EMBOLISM via a persistent foramen ovale is a rare condition, interesting though so uncommon that most experienced physicians have never seen a proved case. Edward¹ states that most cases occur with massive pulmonary embolism and acute cor pulmonale. Very rarely an embolus may lodge in a persistent foramen ovale.

In the case to be briefly described here, there was no pulmonary embolism, and paradoxical embolism occurred twice within less than two days. The pertinent details are as follows:

Mr. S. T., aged 67 years, was admitted to the hospital with severe pain in the left leg below the knee. This had developed suddenly, waking him in the night. On examination the lower left leg was pale and cold, and arterial pulsation was absent below the knee. He stated that for about a week he had had deep tenderness in the right thigh and that the right foot had been intermittently swollen. He had not been examined by anyone previously and there had been no treatment of any sort.

The examining surgeon was certain that the left femoral artery was blocked by an embolus and on surgical exploration such proved to be the case, an embolus measuring 2.3 x 0.8 cm. being found lodged in the popliteal artery.

The embolus was reddish gray in color, very firm and laminated. One end was rounded, the other irregular and jagged, obviously broken off. The patient withstood the surgery well, and circulation to the left leg and foot was restored successfully. There was only slight deep tenderness in the medial right thigh, and there was slight pitting edema of the right ankle. The patient was afebrile.

About thirty-eight hours after this embolectomy was performed, a nurse discovered the patient to be in extremis, ashen and sweating. It was thought that he probably had suffered pulmonary embolism this time. His condition de-

teriorated very quickly, with rapid onset of acute pulmonary edema and with coughing and expectoration of large quantities of foamy fluid. In less than two hours he died.

Postmortem examination confirmed the diagnosis of acute pulmonary edema, but no evidence of pulmonary embolism could be found. On opening the heart, which externally presented some right heart dilatation, an embolus was found lodged in a rather large patent foramen ovale, a cast of a large vessel with two branches. One branch had passed through the foramen and between the leaves of the mitral valve, holding the leaves apart. The other branch had been forced partly through the foramen, so that its mid-portion formed a loop, protruding into the left auricle. The largest portion of the embolus was too large to go through the foramen, remaining in the right auricle, as did the doubled-back end of one of the branches.

Figure 1 is a photograph of the medial side of the right auricle, showing the forked embolus in place.

Figure 2 is a photograph of the medial wall of the left auricle, showing one fork of the em-



Fig. 1. Interior of the right auricle, showing the forked embolus lodged in the Foramen Ovale.

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Fig. 2. Interior of the left auricle showing the embolus protruding from the open Foramen Ovale.

bolus, now shortened and curled during fixation.

Thus the embolus had passed through partially, the passage being stopped when the fork of the branches was reached, somewhat similar to "straddling emboli" sometimes seen at the bifurcation of arteries.

The embolus could be moved readily in the foramen but was not disturbed.

The remainder of the postmortem examination revealed little, except for the findings in the

right common iliac vein. The wall of this vessel was roughened and thickened, over about two-thirds of its circumference. The same process could be seen in the internal and external iliac veins, and sections confirmed the existence of acute phlebitis. A thorough search for other thrombi or emboli was unfruitful. The deep veins of the right leg were studied in detail. Phlebitis of the upper femoral vein was demonstrated microscopically but there were no thrombi in place.

In size and configuration the embolus matched the distal end of the right common iliac vein and its internal and external branches.

COMMENT

Examples of multiple paradoxical embolism are very rare indeed, and instances in which an embolus is found trapped in a patent foramen ovale probably number less than 20.

In this instance, it is believed that both emboli came from the right common iliac vein.

This specimen has been presented to the Pathology Department of the Medical Center at the University of North Dakota.

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PELVIC EXAMINATION of teen-age girls should include cytologic screening for cancer, since overt malignant disease is preceded by a preclinical stage that is both detectable and curable. Of 1,500 females with positive cervical smears, 77 were 14 to 19 years of age. A total of 113 tissue specimens were obtained from 56 girls with positive smears; 25 diagnostic conizations and 70 punch biopsies were done. Intraepithelial cervical carcinoma was diagnosed in 10, only 4 of whom had visible lesions. Dysplasia was found in 20 and cervicitis in 26. Since tissue examination after diagnosis of the positive smear was incomplete in this uncooperative age group, other important cervical lesions probably were overlooked.

J. H. FERGUSON: Positive cancer smears in teenage girls. *J.A.M.A.* 178:365-368, 1961.

Villous Adenoma of the Rectum with Electrolyte Depletion Simulating Adrenal Insufficiency

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VILLOUS ADENOMAS of the rectum and sigmoid are a rare cause of electrolyte depletion. The first case of hyponatremia and hypokalemia associated with electrolyte loss from a large villous adenoma of the rectum was reported by McKittrick and Wheelock¹ in 1954. Since then, 20 additional cases have been described by a variety of authors, thus establishing a well-defined clinical syndrome, which results from the massive secretion with loss of electrolytes from the surface of some large villous adenomas of the sigmoid and rectum. This syndrome consists of azotemia, hyponatremia, hypokalemia, hypochloremia with or without clinical evidence of dehydration, and peripheral circulatory collapse. Four deaths due to uremia, dehydration, and hypotension have been described.²⁻⁵ In spite of the severe hyponatremia that has been present in these cases, very few studies of adrenal function have been done. Schnitka⁴ reported normal urinary 17-ketosteroid and 17-hydroxycorticosteroid levels in a patient in whom autopsy findings showed depletion of total lipids from the zona glomerulosa in the adrenal. This change seemed to resemble the findings in hypertensive patients on a low sodium diet, which are described by Nichols.⁶

This is a report of a case of villous adenoma of the rectum in which the patient presented with attacks of syncope brought on by orthostatic hypotension. Serum electrolyte examination revealed hyponatremia, hypochloremia, and hypokalemia associated with azotemia. In spite of severe hyponatremia, this patient also had a low urinary 17-ketosteroid level and a sustained urinary excretion of sodium. Following

surgical therapy with permanent correction of the electrolyte loss and the return of the serum electrolytes to normal, repeat urinary 17-ketosteroid determinations were normal.

CASE REPORT

A 75-year-old housewife was admitted to St. John's Hospital in Fargo, North Dakota, on July 3, 1960, because of fainting spells. The patient stated she had been well until one week before admission when she fainted while working and fell, bruising her right leg. She stated she had never fainted before and that she had no warning before fainting. Her relatives, who found her unconscious after the fall, said that she recovered within one to two minutes and seemed normal. Since the initial spell, she had had 5 more episodes of syncope, all without warning and all while standing. She denied other neurologic symptoms.

The patient stated she had been well previously except for a fractured right tibia at the age of 14. Family history and social history were non-contributory. She had had shortness of breath on moderate exertion for one year with no angina and intermittent rectal bleeding associated with diarrhea of 2 or 3 stools daily for three to four years. She reported a weight loss of 20 lb. in the last year.

Physical examination revealed a well-developed, fairly well-nourished woman who seemed listless and fatigued. Her blood pressure was 120/70 lying down; pulse rate, 80; temperature, 97.8° F.; and respiration rate, 18. The skin was doughy in consistency. The liver was palpable 1 cm. below the right costal margin, and there were bilateral varicosities of the legs. Rectal examination demonstrated a soft boggy ridge of elevated mucous membrane about 2 in. inside the anus. Examination of the blood pressure

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while standing resulted in an immediate fall in pressure to 60/40, and each time the patient stood erect she fainted. The pulse became weaker during syncope, with a rate of 90. After one to two minutes in the supine position, the patient regained consciousness and seemed normal. The rest of the physical and neurologic findings were normal.

Laboratory examination showed an alkaline urine with a specific gravity of 1.038, a trace of albumin, no sugar, and 2 to 3 white blood cells per high-power field. The hemoglobin was 14.6 gm. or 95 per cent; the white blood count was 9,000, with 77 segmented neutrophils and 23 lymphocytes. The blood urea nitrogen was 68 mg. per cent, serum Na was 125 mEq. per liter, serum K was 3.3 mEq. per liter and the CO_2 combining power was 21.6 mEq. per liter. A chest film showed mild pulmonary emphysema. A roentgenogram of the colon showed some irregularity within the rectum but was otherwise normal. The electrocardiogram showed low-voltage T waves throughout and a prolonged Q-T interval of 0.46 seconds with a sinus rate of 75.

Within three days after admission, the patient seemed weaker, more lethargic, and mentally confused at times. Repeat tests for electrolyte values showed that the serum Na was 115 mEq. per liter; serum K, 3.4 mEq. per liter; and serum chloride, 52 mEq. per liter. Urine examination at this time showed a 17-ketosteroid determination of 1.1 mg. in twenty-four hours; urinary Na, 88 mEq. per twenty-four hours; K, 33.5 mEq. per twenty-four hours; and Cl, 80 mEq. per twenty-four hours.

By the morning of July 8, the patient was acutely ill, semicomatose, and incontinent, her blood pressure fluctuating between 100/60 and 130/70. The blood urea nitrogen had risen to 152 mg. per cent, and repeat electrolyte studies of the serum revealed no change except a drop in the serum K to 2.4 mEq. per liter. At this time, an attempt to do an ACTH test was abandoned and the patient was started on intravenous saline as 5 per cent dextrose in isotonic saline with 40 mEq. of potassium chloride per liter and given 3,000 cc. daily. The patient was also given 100 mg. hydrocortisone intravenously. Within twenty-four hours, she was greatly improved, and, on July 10, the serum Na was 135 mEq. per liter, serum Cl, 90 mEq. per liter, and serum K, 2.6 mEq. per liter. The patient was then given 9-alpha-fluoro-hydrocortisone, 0.1 mg. daily, and cortisone acetate, 50 mg. daily, with extra salt and potassium chloride orally.

By July 16 the patient was ambulatory with no syncopal spells and maintaining her blood

pressure at 130/70. Proctoscopy demonstrated an extensive, soft, polypoid, seaweed-like rectal mass from 3 to 14 cm. within the anus and around the entire circumference of the rectum. Four separate biopsy sites showed no evidence of malignancy. During the patient's entire hospital stay, her bowels moved 2 to 3 times daily; the passage consisted of stool with a large amount of slimy mucus that was frequently tinged with blood. The patient refused surgery and left the hospital. She was discharged on July 20, taking cortisone 20 mg. 2 times a day, 9-alpha-fluoro-hydrocortisone 0.1 mg. daily, and oral sodium chloride and potassium chloride.

The patient was readmitted to the hospital on August 3, 1960, with fainting spells and marked dehydration. Serum Na was 110 mEq. per liter; serum K, 2.2 mEq. per liter; and serum Cl, 57.6 mEq. per liter. She was immediately given intravenous saline with potassium chloride and 100 mg. of hydrocortisone. She again improved rapidly, and, on August 6, serum Na was 132 mEq. per liter; serum K, 2.7 mEq. per liter; and serum Cl, 90.6 mEq. per liter. The blood urea nitrogen was 36 mg. per cent. Her hemoglobin fell from 14.6 gm. on admission to 11.3 gm. after three days on intravenous fluids. By August 11, the patient was maintained on a regular diet with 8 gm. sodium chloride, 3 gm. potassium chloride, 0.1 mg. 9-alpha-fluoro-hydrocortisone, and 50 mg. cortisone taken orally each day. On August 27, a twenty-four-hour collection of rectal mucus yielded 900 cc. This mucus contained 100 mEq. of Na per liter, 35 mEq. of K per liter, and 86 mEq. of Cl per liter. The patient's strength improved, the serum electrolytes remained constant, the blood urea nitrogen returned to normal, and, on September 7, an abdominoperineal resection of the rectum was done.

At operation, a left rectus paramedian incision was used. Exploration of the peritoneal cavity revealed a soft mass in the upper rectal segment. The abdominal portion of the resection was done in the usual way, first dividing the peritoneum along the base of the mesentery and across the anterior rectosigmoid colon. The superior hemorrhoidal vessels were individually ligated and divided. The sigmoid colon was cross-clamped and divided and the colostomy formed lateral to the incision. As is our custom, the internal iliac arteries were ligated in continuity to decrease blood loss. The distal sigmoid colon was dissected off the sacrum. The sigmoid colon was redundant, and a sizable segment was removed. The distal bowel was tied tightly with umbilical cord and placed deep into the pelvis. The pelvic peritoneal floor was constructed and the ab-



The segment of large bowel removed by abdominoperineal resection on September 7.

dominal wound was closed. The patient was placed in lithotomy position and the anus closed. A circumferential incision was made about the anus and the rectal segment completely excised. The perineal wound was closed around Penrose drains. The operation was well tolerated by the patient.

The postoperative period was complicated by a small subcutaneous abscess below the colostomy that required incision and drainage on October 8. Serum electrolytes remained normal after surgery and all adrenal steroids were discontinued by September 21 except for forty-eight hours of cortisone on October 8 and 9 during treatment of the subcutaneous abscess. Urinary 17-ketosteroid levels were 8.4 mg. per twenty-four hours on October 5 and 15 mg. per twenty-four hours on October 16. The patient was discharged on October 17, 1960, and has been followed as an outpatient since. She is asymptomatic, has gained 25 lb., and carries on her usual household work. Her blood pressure remains at 130/70. She was last examined on January 16, 1962.

After the operation, the pathologic examination revealed a segment of large bowel which was 15 cm. long and 10 cm. in its greatest diameter, as shown in the figure. The serosal surface was grayish-red and smooth. On opening the segment, however, the entire surface looked like a bed of lichen or seaweed; in other words, the mucosal surface seemed to be composed of a congeries of papillary projections which had become fused. The mucosa varied from 2 to 3 cm. in thickness. The papillary processes were closely packed, coherent, and flattened at the tips. The papillary projections were sessile or slightly pedunculated, waving gracefully to and fro when the specimen was placed in water. The anus was

present on this portion of bowel and the growth terminated abruptly 2 cm. above the anus. Microscopic examination showed an extensively papillary and glandular growth with wavy and undulated surfaces. The papillary and glandular arrays were lined with hyperplastic, tall, columnar cells that had maintained their polarity well and which exhibited uniform nuclei. The papillary processes had a delicate fibrous stalk and were quite vascular. Most of the cells had a clear cytoplasm and appeared to be actively secreting. The cells were quite swollen. The mucosal basement membrane appeared well outlined. There was scattered round-cell infiltration and no evidence of cellular atypia in several sections from different areas of the bowel. The pathologic diagnosis was villous adenoma of the rectum.

DISCUSSION

Villous adenoma is a well-defined variety of usually large polypous growths of the large bowel characterized by a finely papillary appearance and great vascularity frequently producing bleeding. At times, pronounced electrolyte loss is produced through the mucorrhea. These tumors arise predominantly in the rectum and the rectosigmoid of people of either sex but usually occur in people over 50.^{7,8} The incidence of neoplastic malignant changes varies considerably. This wide variation is due in part to different concepts as to what constitutes significant carcinoma. The changes that may occur are focal cellular atypia, localized malignant changes, and invasive carcinoma. In most reliable series, the incidence of malignant change is about 30 to 35 per cent.⁹ There is a definite tendency to local recurrence. The above-mentioned mucorrhea is not seen in all of these tumors but depends upon the activity of the surface cells, upon hydration of the patient, and especially on the size and surface of the growth. Although the concentrations of Cl and Na ions within the mucus do not deviate from serum levels by more than 30 to 40 per cent, the level of K ion may be as much as 10 times the serum level and has never been reported less than 3 times the serum level.¹⁰

The presenting clinical symptoms in these patients vary greatly. The patients are often accustomed to the copious mucus discharge from the rectum. In the average case, this is present for four to five years before medical attention is sought and the patient may not relate his pseudodiarrhea to the presenting complaint. Abdominal pain, vomiting, anorexia, rectal bleeding, and lethargy are the most common symptoms. In the case reported, the presenting symptom was

syncope due to orthostatic hypotension. The severe hyponatremia with dehydration and contraction of the intravascular volume resulted in a precipitous fall in blood pressure when the patient stood up. Replacement of the electrolyte deficit and rehydration corrected the orthostatic hypotension and allowed the patient to become fully ambulatory.

Because this patient was admitted to the hospital with syncope and minimized her gastrointestinal symptoms, the finding of a severe hyponatremia raised the question of adrenal insufficiency. Few adrenal studies have been reported in this disease. Often the condition of the patient on admission to the hospital necessitates immediate therapy and precludes an intensive investigation. Frequently the patient who has been able to compensate at home by copious fluid and salt intake for the loss of water and electrolytes rectally will decompensate under hospital conditions, particularly if x-ray preparation is necessary. This case demonstrated low urinary 17-ketosteroids and analysis of the urinary loss of Na in the presence of a serum Na of 115 mEq. per liter, showed a continued urinary sodium excretion of 88 mEq. per 24 hours.

With normally functioning adrenal glands, it would be expected that the urinary resorption of Na would be almost complete at the above serum Na level.¹¹ Accordingly the urinary Na values are suggestive for decreased adrenal electrolyte function. Many debilitating conditions can produce a lowering of the urinary 17-ketosteroid levels¹² and the decreased glomerular filtration rate in this patient may have affected the test during this patient's acute illness. Nevertheless, the above values suggest that adrenal response, more particularly aldosterone response, to the hyponatremia and contracted blood volume was insufficient. The occurrence of hypokalemia here suggested that the electrolyte changes were due to the rectal loss of Na and K rather than adrenal insufficiency. Administration of supplementary adrenal steroids failed to control the clinical symptoms until large amounts of Na, K, and Cl were also given.

After removal of the villous adenoma, the electrolytes remained normal without further therapy. Re-examination of the urinary 17-ketosteroid values after recovery resulted in normal values and the patient has remained well since without further therapy. This would establish

that the patient does not have adrenal insufficiency, primary or secondary. At the time of admission, however, this patient may have been in a state of adrenal exhaustion due to the longstanding, constant demand for maximal aldosterone secretion as stimulated by the contracted blood volume and hyponatremia. Transient adrenal insufficiency has been described following suppression of the adrenal with cortisone, and, as mentioned above, low urinary hormone levels can be found in debilitating illness. If transient adrenal exhaustion can occur in this illness, it could contribute to the peripheral circulatory collapse and hypotension that has occurred with this disease. Recognition of this complication would be extremely important in therapy and preoperative preparation.

Definitive treatment of this condition consists of removal of the tumor by appropriate bowel resection. Such villous adenomas as are large enough to cause significant fluid and electrolyte problems will not be amenable to local treatments such as local fulguration and radiation therapy; and so adequate bowel resection must be carried out as a lifesaving measure even though it means, as in this case, a combined abdominoperineal resection of the rectum and a colostomy. The resection need not be radical, but the resection line should be well away from the tumor in depth as well as proximally and distally, because such large adenomas could contain areas of malignancy which might not be disclosed even by multiple biopsies through the sigmoidoscope. Although a major operation is necessary to cure these patients, aggressive medical care is vitally important to get them into satisfactory condition to tolerate the required procedure.

SUMMARY

1. Orthostatic hypotension may be the presenting symptom in patients with a villous adenoma of the rectum with electrolyte depletion.

2. Differentiation of this entity from adrenal insufficiency may be difficult, and in certain cases adrenal exhaustion may complicate the clinical management.

3. Further cases should be studied during the acute phase for evidence of transient adrenal insufficiency as the medical management of the severe hyponatremia and the preoperative preparation of the patient may require the addition of adrenal steroids.

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Doses of thyroid-stimulating hormone (TSH) currently recommended to estimate thyroid status may be fatally excessive in cardiac patients. A man with angina pectoris and a woman with cervical cancer, asymptomatic goiter, and dyspnea and occasional chest pain on exertion died of acute myocardial infarction after receiving 10-unit test doses of TSH daily for two to three days. Postmortem examination disclosed that both had coronary atherosclerosis, the man probably was euthyroid, and the woman had isolated TSH deficiency and lymphocytic thyroiditis.

D. A. BLUMAN: Fatal coronary occlusion following TSH test. *Minnesota Med.* 44:370-373, 1961.

PREMATURE INFANTS grow well for long periods when fed mixtures that provide 3 to 8 gm. of protein per kilogram of body weight daily. Results are not as good when human milk or mixtures providing smaller or larger amounts of protein are fed. Mixtures containing 1.1 to 4.1 per cent of protein were given to 277 premature infants. Babies fed less than 2.5 gm. or more than 8 gm. of protein per kilogram of body weight daily gained poorly, whereas those fed 3 to 8 gm. per kilogram a day gained well. Blood urea nitrogen values remained elevated for as long as six months in babies fed more than 5 gm. of protein per kilogram a day, regardless of birth weight. Stool pH was directly proportional to the amount of protein in the food. Urinary excretion of phenol fell to low values in all babies except those fed more than 5 gm. of protein per kilogram a day. Serum protein values did not differ statistically in infants fed 3 to 8 gm. of protein per kilogram a day, but babies fed less than 3 gm. of protein had low values. Values for weight gain per gram of dietary protein showed better utilization of protein for mixtures with low protein content than for those with high content.

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Pulmonary Blastomycosis:

Case Report of Treatment with Amphotericin B

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THIS IS NOT a deliberate attempt to inundate the medical literature with another case report. Unusual features of this patient with pulmonary blastomycosis and its cure with amphotericin B therapy were deemed by the writer worthy of reporting.

Blastomycosis is unique to North America with the majority of reported cases occurring in the midwest and southern United States. The disease is produced by the doubly contoured, single-budding blastomycosis dermatitides that can be cultured on Sabouraud's media. There is no racial preference, but blastomycosis displays a predilection for the male sex over 50 years of age.¹ No occupation favors development of the disease. Animal infection has not been established as a source, and there are only two animals, the dog² and the horse³ in which blastomycosis occurs as a natural infection.

There are two forms of this disease: (1) primary cutaneous inoculation blastomycosis such as is seen in the laboratory worker, or from the bite of an infected dog;⁴ and (2) systemic blastomycosis, where the disease begins as a primary pulmonary infection from inhalation of the blastomycete.¹⁻⁵ Dissemination to the skin occurs by the hematogenous route and involvement of ribs, vertebrae, and genitourinary system may also occur.⁶ However, it is interesting to speculate, as in the case reported, as to the possibility of the cutaneous lesions about the mouth developing as a result of autoinoculation from the infected sputum.

Pulmonary blastomycosis does not have any symptomatic distinguishing features. It may resemble those of tuberculosis and has masqueraded under this diagnosis. The roentgen aspects of the disease in the thorax are not diagnostic. The pulmonary patterns most frequently seen on the roentgenogram are diffuse miliary involvement, fibrotic lesions as seen in tuberculosis, and homogeneous consolidation.⁷ A high incidence of pleural involvement is also present.

Adequate treatment is dependent upon absolute diagnosis and this is made only by culturing *B. dermatitides* from biopsy material or sputum. Guinea pigs and mice will develop the disease when inoculated intraperitoneally with infected clinical material.⁵ Skin tests with blastomycosis antigens are unreliable.⁸

CASE REPORT

The many facets of systemic blastomycosis involving the lungs are demonstrated in the following report.

H. B., (No. 240964), a 41-year-old white male farmer from Galesburg, North Dakota, was first seen March 17, 1961. He gave the history of having developed the "flu" in December, 1960 and was treated with antibiotics. At this time pleurisy was noted in the right upper anterior chest. Following treatment the patient did well until February, 1961, when he began to tire easily and developed a cough. At this time a chest x-ray was taken and the patient was referred for further investigation. The past history was negative except that a mobile chest x-ray four years previous was negative.

Physical examination elicited an alert, well-developed, adult male; blood pressure 114/84, temperature 99.2, pulse 80. The skin was negative; a small firm mass was palpable in the right supraclavicular area. Auscultation of the chest disclosed a loud expiratory wheeze over the right upper anterior chest. All other physical findings were within normal limits.

The chest x-ray (figure 1) revealed a consolidation of the anterior portion of the right upper lobe inseparable from the superior anterior mediastinum.

Laboratory findings were hemoglobin 11.4 gm., WBC 15,750 with differential of lymphocytes 18 per cent, monocytes 3 per cent, segmented 72 per cent, bands 3 per cent, and eosinophils 2 per cent. The urine examination at this time and all other times was within normal limits.

The patient was hospitalized on March 20, 1961, for further investigation. Findings are summarized as follows: second strength purified protein derivative tuberculin test was negative. Bronchoscopy was negative and a bronchogram failed to reveal filling in the area occupied by the mass in the right upper lobe and suggested its mediastinal origin. Biopsy of the small right supraclavicular mass revealed subacute and chronic lymphadenitis. A total of 9 sputum cultures for fungi were negative. The sputum was negative for acid-fast organisms. The patient by now, either because of the disease or the investigative procedures, had a daily afternoon tempera-

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Fig. 1. Pulmonary blastomycosis showing a homogeneous consolidation of the lung and resembling a tumor mass arising from the right anterior mediastinum

ture to 100° F. It was believed the patient had a mediastinal tumor, possibly a lymphoma, and that exploration was indicated. On April 12, 1961, a right thoracotomy was performed. A consolidation of the anterior segment of the right upper lobe was found which had

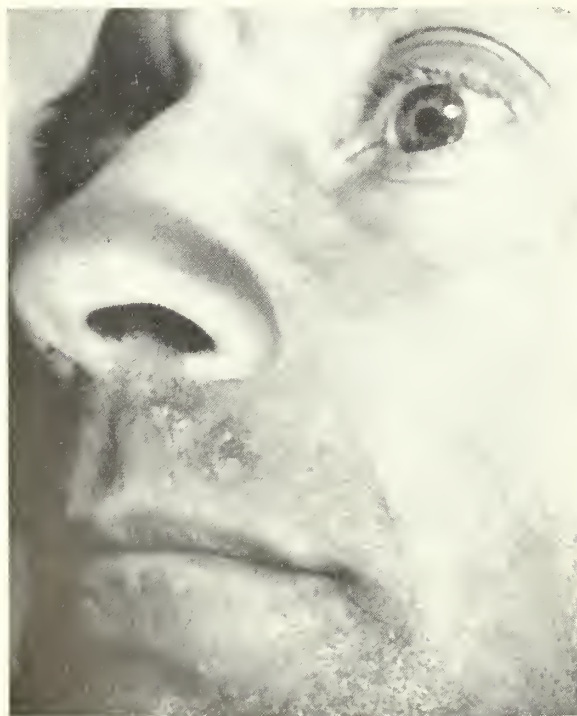


Fig. 2. Skin lesion of blastomycosis developing seven months after initial pulmonary symptoms

rotated anteriorly and become adherent to the superior portion of the mediastinum. The entire upper half of the mediastinum including the hilum was a massive phlegmonous process.

A biopsy was taken from the lung, the cut surface presenting numerous miliary abscesses. Frozen section was reported as a benign nonspecific granulomatous inflammation. Examinations at this time for double contoured bodies and acid-fast organisms were negative. A tuberculous infection seemed most likely at the moment. However, the gross findings and negative tuberculin test did not reinforce this opinion. It was felt that immediate resection in the face of the intense phlegmonous inflammatory infiltration present would be extremely hazardous. Therefore, it was decided to resect at a later date after this patient had been on antituberculous chemotherapy. This ultimately proved to be a wise decision. The post-operative course was uneventful with the patient receiving streptomycin 1.0 gm. and isoniazid 300 mg. daily. He was discharged afebrile from the hospital on the tenth postoperative day. The patient continued on isoniazid and para-aminosalicylic acid at home.

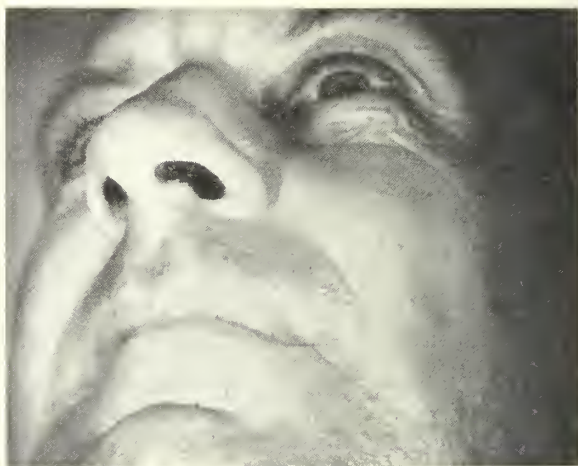


Fig. 3. Healed skin lesion shown in figure 2 one month after amphotericin B therapy

On May 19, 1961, at the time of an office visit, the patient was having night sweats and a small erythematous papulo-nodular lesion had appeared on the left wrist and left nasolabial area (figure 2). Biopsy of the wrist lesion was reported "granulomatosis of skin, probably tuberculous; this most nearly resembles tuberculosis cutis verrucosus." A right-sided pleural effusion developed and was aspirated on May 25 and June 8, 1961, of a turbid, straw colored fluid. This fluid was reported negative on routine culture and a culture for fungi. However, culture was continued and on July 10, 1961, a positive culture was obtained from the chest fluid aspirated on May 25, 1961, for blastomycosis dermatitides.

The patient now entered the hospital for therapy with amphotericin B (Fungizone) intravenously. The drug was given daily intravenously using 90 mg. in 1,000 cc. of 5 per cent glucose in distilled water, taking six hours to administer. This was continued for eleven days for a total dosage of amphotericin B of 1.0 gm. There were no side effects or toxic manifestations. By the fourth day of treatment the facial lesion was decreasing and its resolution could be observed daily. One month after

treatment all skin lesions were healed (figure 3) and the chest x-ray was normal in appearance (figure 4).

On February 6, 1962, the patient returned for a routine checkup. At this time he had gained 15 pounds, enjoyed good health, and was working full time. The skin was clear, and the chest x-ray was negative.

DISCUSSION OF THERAPY

Therapy of blastomycosis until the development of stilbamidine was unsatisfactory, and this drug because of toxicity was of limited value. However, Gold⁹ in 1955 isolated amphotericins A and B from a species of streptomyces obtained from soil near the Orinoco River in Venezuela. Since this discovery amphotericin B has proved to be an effective agent in treating blastomycosis, histoplasmosis, coccidioidomycosis, and cryptococcosis. Abernathy and associates¹⁰ reported 87 per cent prompt healing in the patients with blastomycosis adequately treated with the drug. Amphotericin B is most effective when administered intravenously on successive days, yet it is not without toxic symptoms of which nausea, chills, and fever are most common.

The role of surgery in treating pulmonary blastomycosis is minor. It is the writer's opinion that given a proved case involving the lung, an adequate trial of amphotericin B therapy should be administered before surgery is considered. If pulmonary resection does seem indicated for the rare persistent cavity, the disease should, at that time, be limited to one lung. The results of resection where not supported by chemotherapy are, as revealed by the literature, unimpressive but the courage of the authors admirable. The surgical dilemma arises when one is in the process of operating for an indeterminate lung lesion such as the one reported here. If frozen section reveals a chronic granulomatous lesion appearing as tuberculosis, but in which acid-fast organisms are not readily demonstrated, then the pathologist should take some of the tissue, place on a

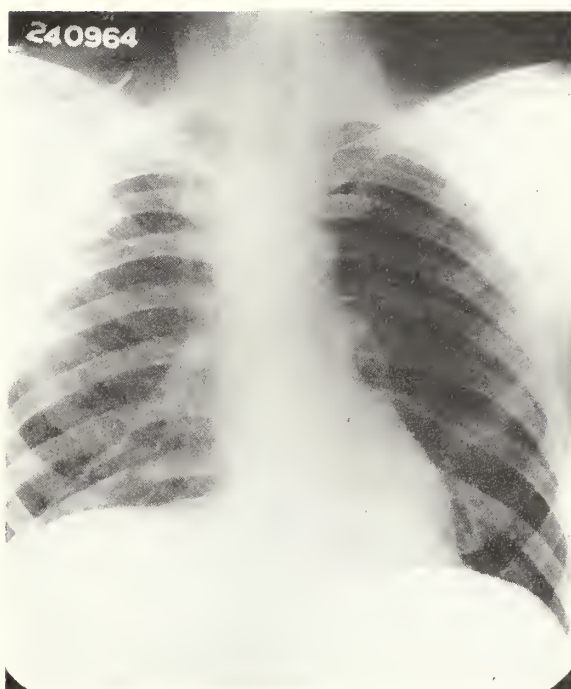


Fig. 4. Complete resolution of pulmonary findings shown in figure 1 one month after completing amphotericin B therapy

glass slide, mix with a drop of 15 per cent potassium hydroxide solution, and heat gently over a flame and examine, using as low a condenser light as possible. This allows visualization of the refractile wall of the single budding blastomycete. If such are found, surgical activity should be terminated, to allow subsequent chemotherapy treatment.

SUMMARY

A proved case of systemic pulmonary North American blastomycosis has been presented together with its care, demonstrating the use of intravenous amphotericin B.

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Cholelithiasis in Childhood and Adolescence

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IT IS WIDELY recognized that in the general population there is a high percentage of cholelithiasis with or without symptoms. This appears to be particularly true of the population in this area. However, the occurrence of cholelithiasis in the first and second decades of life has heretofore been thought to be extremely rare and not a cause of concern in differential diagnosis. The index of suspicion concerning abdominal pain in children seldom points to gallbladder disease, but careful physical examination can often lead one to suspect, and cholecystogram may often confirm, the existence of cholelithiasis in obscure diagnostic problems in children (tables 1, 2).

Potter¹ in 1928 reviewed the literature and popularized the subject to some degree. He emphasized that cholecystic disease in childhood was important and was often overlooked. In 1952 an excellent review of cholecystitis in childhood was made by Ulin and others.² As late as 1958, fewer than 500 cases had been reported in the literature. Many of the reported cases have shown a striking incidence of jaundice and a very low incidence of choledocholithiasis.

Etiologic factors remain obscure. It is well recognized that hemolytic disease often is a source of cholelithiasis, but we will show in our series that this is not a predominant cause. It is frequently recognized that in adult instances, women predominate about 3 or 4 to 1. This ratio does not hold true in childhood cholelithiasis. In our discussion we are speaking only of proved cholelithiasis and disregarding acute cholecystitis. Cholecystitis itself, without cholelithiasis, is found particularly in association with acute infectious diseases, such as peritonitis and meningitis.

We are all aware that acute abdominal symptoms in a child usually lead most clinicians to think of appendicitis rather than a gallbladder condition. This is frequently because of the fact that children localize their pains poorly and because gallbladder disease is so seldom thought of

as occurring in children. However, careful observation and thorough physical examination will soon show that the manifestations of cholelithiasis and cholecystitis vary little in children and adults. When the child is old enough to give a history intelligently, this similarity is quite close. In past reviews of the subject, jaundice has been found to be present in 26 to 45 per cent of childhood cases and 8 to 10 per cent of adult cases of cholelithiasis. Common duct stones, however, have been found in only 6 per cent of childhood patients but have been found in 17 per cent of adults. According to other authorities, the high incidence of jaundice and the low incidence of common duct stones seems to be best explained by a very acute inflammatory process in the gallbladder, which in children lies quite close to the common duct. A proximity of the structures could produce intermittent common duct obstruction. It is conceivable that jaundice is due

TABLE 1
CHOLELITHIASIS IN CHILDHOOD
(UNDER 15 YEARS OF AGE)

Age	Male	Female	Total
6	1	—	1
9	—	1	1
11	1	—	1
13	1	1	2
Totals	3	2	5

Incidence of jaundice in this age group:
1 case out of 5, or 20 per cent.

TABLE 2
CHOLELITHIASIS IN ADOLESCENCE
(15-19 YEARS, INCLUSIVE)

Age	Male	Female	Total
15	—	1	1
17	1	3	4
18	—	6	6
19	1	8	9
Totals	2	18	20

Incidence of jaundice in this age group:
3 cases out of 20, or 15 per cent.

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TABLE 3
QUAIN & RAMSTAD CLINIC

Total number of cases 1948-1960	25
Number of cases proved by surgery	20
Number of cases not proved by surgery but proved by cholecystogram	5
Number of cases with common duct stones	1
All cholecystectomies with proved cholelithiasis 1948-1960	2,489
Cholelithiasis in childhood and adolescence 1948-1960	Approx. 1 per cent

TABLE 4
SUMMARY

Only 2 cases with proved hemolytic disease
One with acute appendicitis, 4 with acute cholecystitis
One with prior diagnosis of abdominal epilepsy
Rarely asymptomatic
Combined gallbladder and stomach x-ray needed in obscure cases of abdominal pain
All except 1 diagnosed prior to surgery
No associated infectious disease at time of diagnosis except for 1 case of appendicitis

to stones which have passed through the common duct, but this seems unlikely, although it is agreed that the stone may pass more easily down the common duct in children than in adults.

Cholecystectomy is still the treatment of choice (table 3). Obviously the need of exploring the common duct is not as urgent as in the adult, but residual stones may be a problem. In particular, we feel that cholecystectomy should be done in childhood for cholelithiasis because of the child's long life expectancy with the possibility of complications, including carcinoma, in the years to come. An early operation by a competent surgeon seems the safest course of management.

Cholecystitis and cholelithiasis in childhood are uncommon but not rare. Certainly choledocholithiasis is rare. However, the possibility should be considered in the differential diagnosis of unexplained abdominal pain and/or jaundice. The clinician should always be alert to further evaluation in cases where an acute abdomen in childhood and adolescence does not give a characteristic picture of appendicitis. If the disease is suspected, the diagnosis is not difficult and in most instances can usually be confirmed by cholecystogram.

It must be emphasized, however, that in the presence of jaundice, an especially careful differential diagnosis must be made so that hepatocellular jaundice will not be confused with cholelithiasis. Ill-advised surgery in infectious hepatitis could lead to an increased mortality.

CONCLUSION

We believe that the concept that cholelithiasis in childhood and adolescence is usually due to an infectious or active hemolytic process is not borne out by this series of cases (table 4). Certainly conservative therapy in the presence of proved cholelithiasis does not appear warranted in view of the contemplated longevity of the individual and the possibility of future complications. Cholecystectomy remains the treatment of choice. The clinician must constantly be aware of the significance of symptoms in this age group to prevent delay in diagnosis. Errors in diagnosis have been frequent, and cholelithiasis in the past has often been found by accident. A need for greater awareness of this condition in younger age groups seems justified.

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Electrocardiography in the Asymptomatic, Middle-Aged Male

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ROUTINE ELECTROCARDIOGRAPHY in asymptomatic, middle-aged males reveals a high incidence of significant abnormalities. It is the purpose of this report to fill a hiatus in our systemized knowledge of routine electrocardiography in apparently normal men of this age group. Earlier reports have been concerned with younger men in military service,¹⁻⁶ and a recent symposium has added a large measure of knowledge to this subject.⁶

METHODS AND MATERIALS

A group of 1,000 asymptomatic male railroad employees with an average age of 50.7 years received a routine 12-lead electrocardiogram. A careful history was taken and complete physical examination performed. None of these individuals had symptoms referable to the cardiovascular system. No murmurs of any type were heard upon auscultation of the heart. Their occupations varied from sedentary to extremely vigorous types of work. All electrocardiograms were read by the author on 2 occasions several months apart. They were initially read in the uncut state.

This group was divided into normotensive and hypertensive subgroups on the basis of a random blood pressure determination. If the blood pressure was above 160 mm. Hg systolic and/or 100 mm. Hg diastolic, the subject was considered hypertensive for purposes of this study. It is realized that this is an arbitrary grouping, since some of the individuals in the hypertensive group did not have clinical evidence of hypertensive vascular disease and the duration of hypertension was not known.

Further subdivision of the hypertensive group was undertaken according to the value of diastolic blood pressure. If this was above 100 mm. Hg the individual was considered a diastolic hypertensive. Also, if a random urine sugar test

was positive, a 3-hour oral glucose tolerance test was done. This group was then divided into diabetic and nondiabetic patients on the basis of established criteria for the diagnosis of diabetes mellitus from a glucose tolerance test.⁷

Electrocardiographic abnormalities were classified according to criteria listed in a standard textbook of electrocardiography. These criteria in their entirety are not necessarily those used personally but are widely accepted and are a convenient reference for this study.⁸

RESULTS

Of the 1,000 individuals included in this study, 235 were considered to be in the hypertensive group. Among these, 105 were diastolic hypertensives. A high incidence (4.1 per cent) of proved diabetes mellitus was encountered (table 1).

Electrocardiographic abnormalities of all types were recorded in 31.5 per cent of the entire group, 23.4 per cent of the normotensive group, 57.9 per cent of the hypertensive segment, 63.8 per cent of the diastolic hypertensive group, and 41.5 per cent of the diabetic patients. The results of this study are collected in table 2. If one excludes premature ventricular systoles of all types from the abnormal classification, the incidence of abnormalities is, of course, lessened.

Coronary artery disease was noted in a significant proportion of middle-aged men. The diagnosis of coronary artery disease was based on established criteria. It is to be re-emphasized that the individuals included in this study were asymptomatic upon cardiovascular system re-

TABLE 1
SUBDIVISIONS OF 1,000 CONSECUTIVE ASYMPTOMATIC
MIDDLE-AGED MALE PATIENTS

Normotensive	765
Hypertensive	235
Diastolic hypertensive	105
Diabetes mellitus	41

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TABLE 2
THE INCIDENCE OF ELECTROCARDIOGRAPHIC ABNORMALITIES (PER CENT)

Type	Entire group	Normotensive	Hypertensive	Diastolic hypertensive	Diabetic
All types	31.5	23.4	57.9	63.8	41.5
Excluding premature systoles	19.6	14.2	23.8	44.8	26.8
Coronary disease	1.8	0.8	3.0	2.9	12.2
a. Infarction	0.9	0.1	2.1	2.9	9.8
b. Ischemia	0.9	0.8	0.8	0	2.4
Bundle branch block	2.7	2.2	4.3	4.8	0
a. Right	1.8	1.7	2.2	2.9	0
b. Left	0.9	0.5	2.2	1.9	0
Premature systoles	11.9	9.2	20.8	19.8	14.6
a. Ventricular	9.0	8.2	11.1	9.5	14.6
b. AV nodal	0.8	0.3	2.6	1.9	0
c. Atrial	1.2	0.7	3.0	4.8	0
d. Combined	0.7	0.1	2.6	2.9	0
Left ventricular hypertrophy	0.3	0.2	0.1	0	0
Suggesting LVH	6.8	3.7	17.5	15.1	7.0
Left ventricular "strain"	0.8	0.3	2.6	3.8	0
Nonspecific T-wave changes	7.6	3.9	20.0	28.6	15.6
Coronary sinus rhythm	0.5	0.3	1.3	1.3	0
1° AV block	0.9	1.0	0.9	0.9	2.4

view at the time of the study and in the past. Of these 1,000 subjects, 18 had conclusive electrocardiographic evidence of coronary artery disease. Changes that were typical for a myocardial infarction were present in 9, whereas the other 9 demonstrated evidence of myocardial ischemia. Myocardial ischemia was located anteriorly in 7 patients and posteriorly in 2. Myocardial infarction patterns were posterior in location in 3, posterolateral in 5, and anterolateral in 1. Therefore, a ratio of 8 posterior infarctions to 1 anterior infarction was present in these asymptomatic individuals. However, in a series of 10,000 electrocardiograms taken under varying circumstances and read by the author, the incidence of posterior myocardial infarction to anterior myocardial infarction was 1.6:1. Only once was a myocardial infarction recorded in a normotensive, nondiabetic individual.

Bundle branch block was present in 2.7 per cent of the entire group and in 4.3 per cent of the hypertensive group. Right bundle branch block was twice as common as left bundle branch block in the group as a whole, but the distribution was equal in hypertensive individuals. Right bundle branch block was incomplete in 4 patients and complete in 14 (2 of these had the intermittent type). No tracing was read as an incomplete left bundle branch block. Only 1 example of intermittent complete left bundle

branch block was encountered in the 9 tracings classified as complete left bundle branch block.

Premature ventricular systoles comprised 37.8 per cent of all abnormalities classified. It can be noted from table 2 that there was a somewhat greater incidence among hypertensive and diabetic subjects than in normotensive individuals. Of these premature beats, 75.6 per cent were of ventricular origin. They were present on 90 tracings; 82 were unifocal, 5 were multifocal, 2 were bidirectional, and 1 was interpolated. It is of additional interest to comment on 2 asymptomatic individuals who demonstrated unifocal sequential ventricular premature systoles in sequences of 2 to 4 beats. After a year of follow-up, neither of these 2 subjects had manifested symptoms of cardiovascular disease and no recurrence of sequential premature beats was detected.

Premature ventricular systoles of supraventricular origin or combined with beats of ventricular origin were significantly more common in the hypertensive group than in the normotensive one, whereas those of ventricular origin were about equally divided between the 2 groups. A tracing of atrial bigeminal rhythm was recorded in a normotensive, nondiabetic subject.

A typical left ventricular hypertrophy pattern that met the rigid criteria outlined for this diag-

TABLE 3
INCIDENCE OF ELECTROCARDIOGRAPHIC
ABNORMALITIES (PER CENT)

Atrial fibrillation	0.2
Wolff-Parkinson-White syndrome	0.2
Wandering pacemaker	0.1
Abnormal P waves	1.1
R/S > 1	0.4
R wave V ₁ > 5 mm.	2.2
Low voltages	2.3
Tall T waves	0.4

nosis was seen only 3 times. Interestingly, 2 of these 3 were in normotensive individuals, and all 3 were associated with the characteristic T-wave changes of left ventricular "strain." Electrocardiographic patterns that are suggestive of left ventricular hypertrophy by voltage increases but do not meet the rigid criteria diagnostic of left ventricular hypertrophy were present on 68 tracings. There was an incidence of 3.7 per cent in the normotensive group, 17.5 per cent in the hypertensive group, and 15.1 per cent in the diastolic hypertensive group. Characteristic isolated left ventricular "strain" was noted 8 times (6 hypertensive and 2 normotensive individuals). Other T-wave changes that are nonspecific in type comprise a nebulous group. The criterion for inclusion in this group was a T-wave voltage decrease to less than 10 per cent of the height of the QRS complex in leads arising from the left ventricle. Such changes were present in 3.9 per cent of normotensive individuals and in 20 per cent of the hypertensive group. They were noted in both leads V₅ and V₆ a majority of the time but almost as often in the combination of leads I, aVL, V₁ through V₆. First degree AV block was not more frequent in hypertensive individuals, but coronary sinus rhythm was decidedly more common in the hypertensive group. Second-degree and complete AV block were not seen.

Various other miscellaneous abnormalities were recorded (table 3). Atrial fibrillation was noted on 2 occasions in symptom-free individuals. A wandering atrial pacemaker was noted once and a typical Wolff-Parkinson-White syndrome twice. Abnormal P waves were recorded 11 times. The abnormality in the P wave was usually that of a duration greater than 0.11 second and was most often noted in normotensive subjects. A general decrease in all voltages was seen without clinical evidence of obesity or pulmonary emphysema in 12 patients. Tall peaked T waves in precordial leads were present without clinical reason on the 4 occasions listed.

Some interest has been expressed in the use of an R wave in lead V₁ greater than 5 mm. as a criterion for the diagnosis of right ventricular preponderance. This situation was encountered 22 times—4 times in hypertensive individuals, 4 times in markedly obese patients, twice with kyphoscoliosis, twice with considerable pectus excavatum, and 14 times without clinical reason. An R/S ratio greater than 1 was seen 4 times, twice in markedly obese individuals.

SUMMARY

Routine electrocardiography in the asymptomatic middle-aged male is an eminently productive clinical procedure, even though criteria for the diagnosis of an abnormality are conservatively applied. In this study, it was found that about 2 of every 100 males who had no past or present history of heart disease had conclusive electrocardiographic evidence for coronary artery disease.

Also of significance is the fact that silent myocardial infarction is more often located on the posterior surface of the left ventricle than on the anterior surface and is a common occurrence in patients who have diabetes mellitus. Almost all abnormalities are more commonly noted in individuals who have hypertensive blood pressure levels; nearly 25 per cent of middle-aged males had hypertension on random blood pressure sampling; and over 10 per cent had a diastolic hypertension.

Among all individuals in this study, 31.5 per cent had abnormalities of some type on their electrocardiograms. This incidence was increased to 63.8 per cent in the presence of diastolic hypertension and to 41.5 per cent when diabetes mellitus was associated. The incidence of proved diabetes mellitus was 4.1 per cent.

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Feigned Insulin Reactions in Diabetic Children Prevented by Glucagon

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MURLIN and associates¹⁻³ were the first to prepare an insulin-free pancreatic extract possessing hyperglycemic properties. They coined the appropriate term glucagon for this substance. It was presumed but not conclusively proved to be produced by the alpha cells of the pancreas. Burger and co-workers⁴⁻⁸ shortly thereafter were able to demonstrate that the initial transitory hyperglycemic effect of the injection of most insulin preparations was due to the presence of small amounts of glucagon. This observation implies that glucagon exerts its effects with dramatic, though transient, rapidity compared with the relatively slow onset of insulin action. It follows that glucagon should thereby prove invaluable in the treatment of the insulin reaction, for in the latter phenomenon rapid reversal is of prime importance.

Among the very few conditions in human beings in which the hyperglycemic potential of glucagon is more or less nullified are depletion of liver glycogen, thyrotoxicosis, and enzyme deficiency preventing glycogenolysis, such as one encounters in deficiency of glucose-6-phosphatase in von Gierke's disease.⁵ Glucagon is totally ineffective in phenformin-induced hypoglycemia. In the absence of these conditions, glucagon in appropriate dosage invariably exerts hyperglycemic effects in both diabetics and nondiabetics. Since it is still present in most commercially available insulins, the transient hyperglycemia noted after an insulin injection in many diabetic patients whose liver glycogen reserves are intact cannot be avoided. It has been pointed out that insulin and glucagon should not be regarded as antagonists but rather as synergists, since in the mutual metabolic interaction of glucagon and insulin the specific function of glucagon is to provide the peripheral muscles with glucose

when necessary by splitting off hepatic glycogen, the oxidation of which may then be aided by insulin.⁹ It is believed that glucagon increases hepatic glycogenolysis by effecting the transformation of inactive hepatic phosphorylase into its active form. Paradoxically, it has been shown that repeated administration of glucagon in rabbits and rats increases hepatic glycogen reserves.

Before their commercial release, few drugs have been subjected to more exhaustive investigation than glucagon, which is documented by well over 550 publications. Its use as an emergency drug for the termination of insulin hypoglycemia has proved singularly innocuous. It has gained wide acceptance for the termination of insulin coma therapy in schizophrenic patients. Indeed, Esquibel and Kurland¹⁰ encountered only 7 failures in 2,475 terminations. The total absence of untoward reactions further confirmed the high degree of safety with the use of glucagon. Generally, the average awakening time was about fifteen minutes, after which patients responded verbally to questions and were able to take fluids orally. Contrary to the use of intravenous glucose with its cumbersome technique, local irritation, and not infrequent venous sclerosis, glucagon could be administered in much smaller quantities (2 to 5 mg. or 2 to 5 cc.) with ease, either intravenously or intramuscularly.

Staub, Sinn, and Behrens,¹¹ working in the Lilly Research Laboratories, not only purified and crystallized glucagon but clarified its physiologic differences from insulin. Further brilliant research by Lilly investigators established the chemical structure of this complex protein molecule.¹²

The modern trend toward early marketing of experimental drugs is certainly not exemplified by glucagon, which, if anything, might have been released earlier and more safely than most drugs. This conservatism is a tribute to Eli Lilly and Company who currently manufacture glucagon for clinical use as the culmination of over

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thirty-eight years of research by domestic and foreign investigators.

PLAN OF INVESTIGATION AND OBJECTIVES

Numerous favorable reports on the successful termination of hypoglycemic shock and coma, coupled with successful reversal of 122 insulin reactions in the author's experience among private diabetic patients, served as an inducement to initiate clinical trials of glucagon during the years 1960 and 1961 at Camp Sioux, a free summer camp for diabetic children operated since 1953 by the North Dakota Diabetes Association, Inc. Since the age range of campers (8 to 15 years) was the same each year and the total enrollment nearly the same, it was decided that our over-all experience during the 1959 camp session would provide a satisfactory control for glucagon studies carried out during the subsequent two years.

At the outset of each of the 1960 and 1961 camp sessions, the children were informed that every insulin reaction, regardless of severity, would be treated with an intramuscular injection of glucagon, followed after fifteen minutes by 3 or 4 Dextrotabs,* 2 graham crackers, and a glass of milk. Children were divided according to weight into 2 groups—those weighing 80 lb. (36.4 kg.) or over and those under 80 lb. Any reaction among those in group 1 was treated with a dose of 2 mg. (2 cc.) of glucagon while any reaction in group 2 was treated with 3 mg. (3 cc.).

During the day, 2 graduate nurses experienced in diabetic care and 3 student nurses were in constant attendance to recognize the earliest possible signs of hypoglycemic shock. These

nurses alternately made rounds several times each night so that it was virtually impossible for even the slightest reaction to evade detection. Further precautions included a priority classification of campers who were reaction-prone and as such were under closer surveillance.

Objectives of clinical trials of glucagon for hypoglycemic reactions were as follows: (1) to determine the frequency of treatment failures in reversal of insulin reactions; (2) to establish the minimum, maximum, and average reversal time after injection; (3) to compare the effects of glucagon treatment of hypoglycemic reactions with those of sugar ingestion on diabetic control; and (4) to compare the frequency of hypoglycemic reactions occurring during the camp session of 1959 with those of 1960 and 1961.

RESULTS

There was a dramatic decline in frequency of insulin reactions from a total of 95 in 1959 to totals of 11 and 8 for the 1960 and 1961 seasons, respectively (table 1). Whereas every child suspected of having even the slightest insulin reaction was treated with oral glucose (Dextrotabs) in 1959, none received this treatment without an initial injection of glucagon during the 1960 and 1961 seasons. Among 12 campers who attended all 3 camp sessions, the total number of reactions declined from 46 in 1959 to 7 and 4, respectively, for 1960 and 1961.

Glycosuria was estimated 4 times daily for each camper by the Clinitest method. In table 2 it will be noted that to simplify interpretation of results, the single urine test recorded for each day actually represents the average of 4 tests performed, graded on the basis of 0 to 4+. Furthermore, at the end of the seven-day camp session, a grand average urine test is recorded for each of the 12 campers who attended in 1959, 1960, and 1961, respectively. Utilizing this technic, 9 of the 12 campers who attended all 3 seasons exhibited slight to marked improvement in glycosuria during 1960 and 1961 compared with that shown for 1959. In the entire group, 1 patient (patient 4) exhibited slightly more glycosuria in 1960 but distinctly less during 1961 than during the 1959 control season. Another patient (patient 5) was sugar-free during the 1959 and 1960 seasons but exhibited moderate glycosuria during the 1961 season. The remaining patient (patient 9) was persistently sugar-free throughout all 3 camp sessions. (The average for each seven-day period was carried out to 2 decimal places to facilitate more precise comparisons.)

The frequency and severity of hypoglycemic

TABLE 1
FEIGNED INSULIN REACTIONS IN A DIABETIC
CHILDREN'S CAMP
(Twelve children attended three seasons)

<i>Camp season</i>	<i>1959</i>	<i>1960</i>	<i>1961</i>
Number of campers	33	37	38
Age range (years)	8-15	8-15	8-15
Number of insulin reactions throughout camp session	95	11	8
Reactions treated with oral sugar only	95	None	None
Reactions treated with glucagon intramuscularly	None	11	8

Conclusions: (1) Vast majority of reactions in 1959 were feigned.
(2) Parents should be aware of this possibility in their diabetic children.
(3) Physicians should advise trial of glucagon for suspicious cases.

reactions observed in this group are tabulated in table 3. Reactions were graded on the basis of IV, as described in the legend. Accordingly, a total of 46 reactions occurred during the 1959 season, all classified as grade I except for a single grade II reaction. In contrast, 7 reactions occurred in 1960, 3 being grade I and 4 being grade II, while 4 reactions occurred in 1961, all being grade II. All reactions responded promptly to intramuscular glucagon administered in dosages previously outlined. The minimum time required for total reversal of hypoglycemic symptoms was two minutes, the maximum time being eight minutes. The average time required for complete reversal among the total of 19 insulin reactions was four and one-half minutes. As might be expected, grade I reactions responded more rapidly than grade II.

COMMENT

While it is a tribute to the camp personnel that no hypoglycemic reactions were permitted to progress beyond grade II during any of the 3 seasons, the inordinately high frequency of such reactions during the 1959 session was obviously due to deception of the professional staff, consisting of 2 registered nurses, 3 senior student nurses, and 7 volunteer camp physicians (the latter serving one day each as "camp physician"). The author, as chairman of the camp professional committee, visited the camp each evening to review the day's clinical records and, therefore, accepts full responsibility for our over-all deficiency of clinical acumen in failing to recognize that a high percentage of these so-called reactions were feigned in a "tricks or treats" maneuver! However, it is perhaps beyond mere rationalization on our part to emphasize that nearly all reactions, whether actual or feigned, were brought to the staff's attention (by the camper himself) after vigorous exercise which, of course, results in perspiration—a frequent concomitant of even early hypoglycemic shock. Obviously, too, the majority of spurious reactions could have been readily screened out by awaiting more precise signs of hypoglycemia or performing blood sugar tests on the spot, or both. The latter recourse would hardly have been practicable at some distance from the dispensary and the not infrequent occurrence of more severe legitimate reactions served as a further deterrent to procrastination in treating patients with those convenient 2, 3, or 4 Dextrotabs. In fairness to the camp staff it should be further stated that the pronounced increase in frequency of reactions occurring during the 1959 session (in sharp contrast with the 1958 total of 56 reactions) con-

vinced all of us, in retrospect, that surreptitious forces were at work! Curiously, not a single camper objected to glucagon treatment of the few reactions occurring during the 1960 and 1961 seasons—rather convincing evidence that we had now sifted the "true" from the "false" reactions.

In an effort to establish valid comparisons of our experience with insulin reactions with that of other diabetic children's camps, a questionnaire was sent to 10 such camps. Only 4 responded and of these only 2 could be used for statistical comparison. None of the camps had used glucagon. One camp averaged 35 insulin reactions per week, 3 reaching the coma stage (grade IV), among 80 children in attendance. The other camp averaged 23 reactions, none reaching the coma stage, among 47 children. While, admittedly, the frequency of reactions in these 2 camps is far below that for our 1959 camp session, it is considerably greater than the incidence during either our 1960 or 1961 session (table 4). It would be most interesting to observe the experience of these 2 camps if glucagon were used exclusively for all reactions.

Finally, while this report is in some respects an exposé of our inadequacies, it is nevertheless charged with some ammunition against the guiles which I have seen more than one child implement against his parents, whether as a weapon, an attention-getting device, or a simple craving for sweets. The object lesson of our experience at the camp should be obvious: The clinician who suspects this "tricks or treats" tactic in a juvenile diabetic would do well to instruct the parents to use glucagon exclusively for all reactions occurring over a given period, not as a punitive measure but rather to establish "who is kidding whom." With this approach, the clinician may thus stabilize a seemingly "brittle" juvenile diabetic, enhancing the prevention of subsequent complications in addition to releasing the parents from the misery of endless apprehension and frustration.

Throughout this study not a single reaction failed to respond to glucagon. While dosages of 2 to 3 mg. (2 to 3 cc.) are in excess of the 1-mg. (1-cc.) dose recommended by a number of investigators, the latter dosage has proved totally ineffective in certain unpredictable cases. Among 122 hypoglycemic reactions in adults treated by the author,¹³ there were 8 failures, 6 of which resulted from 1-mg. (1-cc.) doses and 2 from 2-mg. (2-cc.) doses of glucagon. All other patients were given 3- to 4-mg. doses with uniform success. Since hypoglycemic shock is a potential medical emergency, one should not risk in-

TABLE 2
AVERAGE DAILY GLYCOSURIA (CLINITEST) EXHIBITED BY EACH OF
12 CAMPERS WHO ATTENDED ALL 3 CAMP SESSIONS

Patient	1959								1960								1961							
	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	Average test for 7 days	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	Average test for 7 days	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	Average test for 7 days
1	3	2	2	0	4	4	4	2.43	2	1	2	3	1	3	1	1.85	1	1	1	3	3	2	0	1.57
2	0	2	2	1	0	1	1	1.00	1	1	1	0	0	0	0	0.42	0	0	0	0	2	1	0	0.42
3	4	3	4	2	1	4	2	3.28	3	1	1	1	3	1	1	1.57	4	4	3	2	3	4	3	1.57
4	3	2	0	2	2	2	3	2.00	3	2	2	3	2	2	1	2.14	3	2	1	2	1	1	1	1.57
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	1	1	1	0	3	3	1.71
6	1	0	2	2	2	3	3	1.85	4	0	0	1	0	1	0	0.85	2	2	0	3	2	1	0	1.42
7	2	1	0	0	2	3	3	1.57	0	0	1	0	0	1	1	0.42	0	0	0	0	0	0	0	0
8	3	3	3	1	2	4	4	2.85	3	2	0	3	3	1	3	2.14	2	0	0	3	3	2	2	1.71
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	3	2	1	2	2	2	2	2.00	0	1	0	0	1	2	1	0.71	0	0	1	2	2	2	2	1.28
11	2	1	2	0	0	2	3	1.42	2	1	1	0	1	1	0	0.85	0	0	2	2	1	3	1	1.28
12*	4	0	4	4	4	4	4	3.42	4	3	3	3	3	3	3	3.14	3	3	2	4	4	3	2	3.00

Since every camper was tested 4 times daily, each recorded test above represents an average of 4 tests. Also included is the grand average urine test, carried out to the second decimal place, for the entire week. (Glycosuria is graded as 0, 1+, 2+, 3+, and 4+.)
*Patient 12 represents a low renal threshold diabetic.

adequate dosage in the use of glucagon, implementing the philosophy that giving a little too much is far safer than not enough. While the chronic administration of glucagon can effect major metabolic alterations such as increased nitrogen excretion, diminished creatinuria, ketonuria, nausea, and vomiting, no serious effects of 1 dose have been reported except for the single case of hypotension following rapid intravenous injection and probably representing a sensitivity reaction.¹⁴ The current availability of more purified crystalline preparations greatly diminishes this possibility.

One of the many advantages of glucagon is that diabetic control is not upset, since the maximal arterial glucose level reached after a single injection is well within the normal postprandial range of 153 mg. per cent.¹⁵ Feedings which follow glucagon treatment of hypoglycemia should be prompt but conservative. Even in cases of insulin coma, an adequate postinjection feeding consists of 3 or 4 Dextrotabs (or 150 to 200 cc. orange juice) and a light meal given as soon as the patient can swallow. Prolonged cumulative hypoglycemic coma from modified insulins demands more aggressive measures¹⁶ and will not be discussed here.

Following injections of glucagon, the rather prompt total reversal time (averaging four and

one-half minutes) was, of course, due to the absence of any severe (grade III to IV) reactions.

Comparison of diabetic control during the 1960 camp session with that during the 1960 and 1961 sessions (table 2) clearly indicated the salutary effects of the use of glucagon. This is most dramatically illustrated by patient 3 who was treated for 11 "reactions" in 1959 compared with a total of only 2 and 1 during the 1960 and 1961 seasons, respectively. As a result, his glycosuria diminished more than 50 per cent and his insulin requirement more than 25 per cent during the 1960 and 1961 seasons. The average daily insulin requirement per child fell from 40.2 units to 30.0 units (a 25 per cent decrease) in the group of 12 patients who had attended both 1959 and 1960 sessions. The average dosage for 1961 is omitted from this study since two years of growth in young children hampers logical interpretation of results. Throughout all 3 camp sessions there were no instances of impending ketoacidosis, and, in fact, a review of each camper's records prior to entering camp indicated that diabetic control was at least as good as and usually better than had been achieved at home.

Glucagon has recently been marketed in lyophilized form to permit a longer "shelf life." In this state it remains stable almost indefinitely until reconstituted, after which the manufacturer

TABLE 3
INSULIN REACTIONS

Patient	1959 Grade of reaction				1960 Grade of reaction				1961 Grade of reaction			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
1	4				1	1						
2												
3	10	1				2				1		
4	4				1							
5	2											
6	5				1							
7	3					1				3		
8	2											
9	4											
10	4											
11	3											
12	4											
Totals	45	1			3	4				1		

Note that insulin reactions are graded on the basis of IV as follows:

Grade I: Slight, barely detectable as sweating, anxiety, tremor, numbness, tingling, etc. (usually the patient self-diagnosing for the physician)

Grade II: More precise and severe than grade I (easily detected by the physician)

Grade III: Severe symptoms and signs with confusion

Grade IV: Unconsciousness (see text for explanation)

advises it be used within one month.¹⁷ As yet, however, the actual stability time in solution remains to be established. It is obviously most cumbersome to reconstitute glucagon under emergency conditions where time is of the essence. It has been our policy at the Grand Forks Clinic to store glucagon in solution for immediate use at any time, and patients and their relatives have been instructed to do likewise. We are convinced that such solutions retain their full potency for at least one year, judging from the clinical efficacy of solutions over one year old. The date of reconstitution should always be recorded on the label. In treating insulin reactions at home, relatives of diabetic patients are taught to administer 2 or 3 syringefuls, hypodermically, in as many different areas of the body, utilizing the patient's 1-cc. insulin syringe. This has proved highly successful. No reaction-prone patient (unless he lives alone) should be without a bottle of glucagon in his home refrigerator. This is especially true in rural areas where one might become snowbound, in which case severe, prolonged, cumulative hypoglycemic coma may pose a threat to life.

SUMMARY AND CONCLUSIONS

Glucagon was used to terminate any and all hypoglycemic reactions occurring in a diabetic children's camp during the years 1960 and 1961. The very low frequency of reactions occurring during these 2 camp sessions is sharply contrast-

ed with a very high occurrence rate for the preceding (1959) camp season, during which glucose and other feedings provided the sole form of therapy. The exclusive use of glucagon during the subsequent 2 camp sessions served to confirm a suspected high incidence of feigned insulin reactions occurring during the 1959 camp session.

Clinical data from among the 12 children who attended all 3 camp sessions are assembled for statistical comparison, as illustrated in tables 2 and 3. While the frequency of insulin reactions occurring in 2 other diabetic children's camps were obviously much lower than in our camp during 1959, their incidence was considerably higher than we recorded during 1960, indicating

TABLE 4
INSULIN REACTIONS (PER CAMPER, PER WEEK) IN 3
DIABETIC CHILDREN'S CAMPS

	1959 Reactions	1960 Reactions	1961 Reactions
Camp "A"	Not available	.437 (No glucagon)	Not available
Camp "B"	Not available	.489 (No glucagon)	Not available
Camp Sioux	2.878 (No glucagon)	.297 (Glucagon)	.210 (Glucagon)

While the frequency of reactions is inordinately high for Camp Sioux during the 1959 session, note the sharp decline in frequency during 1960 and 1961. In contrast, the experience of 2 comparable camps during 1960 indicates a decidedly higher occurrence when glucagon is not used.

that a number of these may also have been feigned (table 4).

From these observations the following conclusions appear to be justified:

1. The occurrence of feigned insulin reactions among juvenile diabetic patients is no doubt more common than previously supposed. Whether they represent a weapon, an attention-getting device, or a simple craving for sweets, the physician who suspects this "tricks or treats" tactic should instruct parents in the exclusive use of glucagon over a given period in an effort to clarify the issue.

2. Beyond these advantages, glucagon is also an unusually safe drug and should be imme-

diately available in the home of the reaction-prone diabetic patient and in the physician's office.

3. Marketing this drug in 1-mg. (1-cc.) vials should be abandoned in favor of minimum dosage vials of 2 mg. in addition to the 10-mg. vials currently available. It is injudicious to risk underdosage with a drug possessing such a wide margin of safety.

The author is grateful to Arlys Underberg, R.N., and Joan J. Hvidsten, B.S., therapeutic dietitian, for valuable technical assistance in this investigation.

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LIKE IPRONIAZID, monamine oxidase-inhibiting drugs, such as pheniprazine, nialamide, and phenelzine, administered to relieve depression can cause hepatitis. Treatment with pheniprazine caused liver damage in 3 patients; 1 of these subjects had previously had iproniazid-induced hepatitis and another had recurrence of jaundice when nialamide was subsequently given. Hepatitis was fatal in 1 patient. In a fourth patient, administration of phenelzine produced hepatic damage. Liver cell necrosis associated with infiltration by inflammatory cells was the main change seen in all the patients.

C. D. HOLDSWORTH, M. ATKINSON, and W. GOLDIE: Hepatitis caused by the newer amine-oxidase-inhibiting drugs. *Lancet* 2:621-623, 1961.

Incidence of Rheumatic Fever

A Four-Year Study Among Incoming Freshmen at the University of North Dakota

EDWIN G. OLMISTEAD, M.D., and KAREN GECK

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A FOUR-YEAR STUDY was undertaken in the fall of 1958 to determine the incidence of previous rheumatic fever in freshmen students entering the University of North Dakota. The purpose of the study was to determine (1) the incidence of a history of rheumatic fever in this population, (2) the incidence of rheumatic valvular heart disease in this group, (3) the number of students with a history of rheumatic fever who were on prophylaxis against the group A hemolytic streptococcus, and (4) the number of recurrences of rheumatic fever in students on prophylaxis as compared with those who were not on prophylaxis.

The University of North Dakota is a state-supported university with an average freshmen enrollment of between 1,100 and 1,200 students. The student body is drawn largely from North Dakota and northwestern Minnesota. The ratio of men to women is about 3 to 1 in the freshmen class. All students entering the university are required to fill out a health form and to have a physical examination by their home physician, usually in the summer preceding entrance to the university. These forms become a part of the student health record.

In the present study, all entering students with a history of rheumatic fever, as noted on the health form, were called to the Student Health Center where a complete history and physical examination were carried out. Chest roentgenograms and electrocardiograms were obtained from all students with valvular heart disease. A few students were not counted in the survey, as the past history of the rheumatic attack was not considered adequate to justify the diagnosis of acute rheumatic fever. In determining the in-

cidence of rheumatic valvular heart disease in freshmen students, only valvular heart disease occurring in students with a history of rheumatic fever was counted for this study. There were instances of valvular heart disease in incoming freshmen which were, undoubtedly, due to a previous attack of rheumatic fever of which the patient had no knowledge.

Incidence of rheumatic fever in incoming freshmen. Figure 1 shows the incidence of rheumatic fever in incoming freshmen for the school years 1958-1961, inclusive. It should be noted that about 2 per cent of incoming freshmen gave a history of rheumatic fever and this percentage was relatively constant over the four-year study.

Incidence of valvular heart disease in freshmen students having a history of rheumatic fever. Figure 2 shows the incidence of valvular heart disease in those students with a history of rheumatic fever. This study demonstrates a striking drop in valvular heart disease in this group from 58 per cent in 1958 to 15 per cent in 1961. It

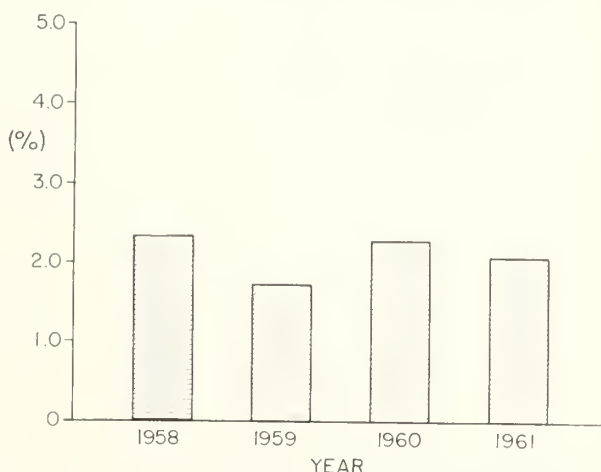


Fig. 1. Per cent of incoming freshmen at the University of North Dakota with a history of rheumatic fever for years 1958-1961.

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Fig. 2. Per cent of freshmen with a history of rheumatic fever found to have valvular heart disease on entering the University of North Dakota for years 1958-1961.

should be emphasized that this drop occurred in spite of the fact that the number of entering students with a history of rheumatic fever remained relatively constant throughout the four-year study.

Number of students with a history of rheumatic fever on prophylaxis at the time of entering the University of North Dakota. Figure 3 demonstrates the increased use of prophylaxis

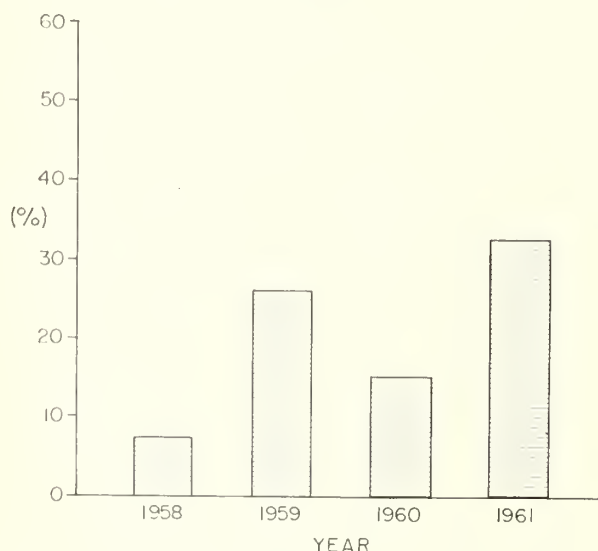


Fig. 3. Per cent of freshmen with a history of rheumatic fever on prophylaxis when admitted to the University of North Dakota for years 1958-1961.

(almost always oral or long-acting injectable penicillin) by physicians in this area for patients with a history of rheumatic fever. Nonetheless, in 1961 only 33 per cent of the incoming freshmen class with a history of rheumatic fever were on prophylaxis against group A hemolytic streptococcus.

Figure 4 shows the percentage of freshmen students with rheumatic valvular heart disease who were on prophylaxis at the time of their admission to the University of North Dakota. This percentage rose from 13 per cent in 1958 to 100 per cent in 1961.

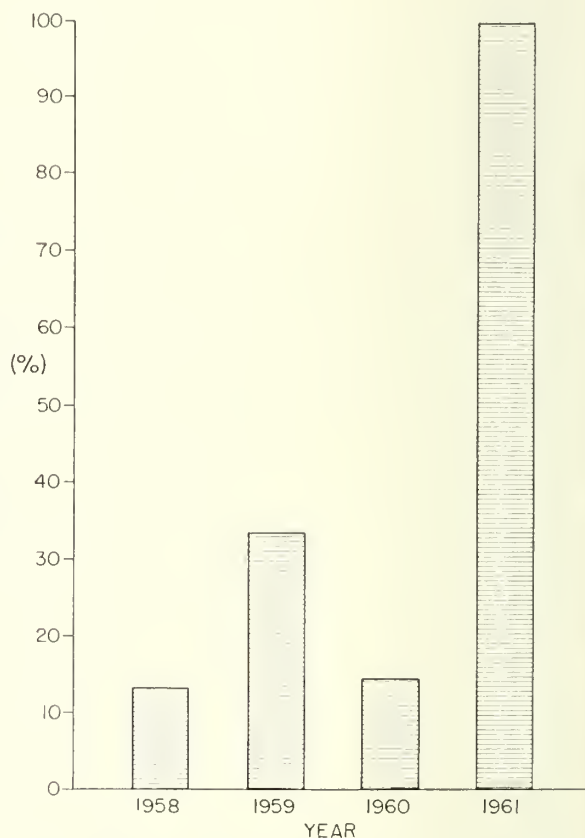


Fig. 4. Per cent of freshmen students with a history of rheumatic fever and valvular heart disease on prophylaxis when admitted to the University of North Dakota.

Table 1 formulates the four-year statistics concerning rheumatic fever in freshmen students in this study and table 2 lists the types of valvular heart disease found in those incoming freshmen with a history of rheumatic fever.

In the national report on the incidence of rheumatic fever in college freshmen, Sandridge and associates¹ found an incidence of 2.5 per cent of definite or questionable rheumatic fever. This is not significantly different from the 2.2

TABLE 1
SUMMARY OF FOUR-YEAR STUDY
OF FRESHMEN STUDENTS WITH HISTORY OF
RHEUMATIC FEVER

	<i>Number of freshmen</i>	<i>Per cent of total freshmen</i>	<i>Per cent of freshmen with rheumatic fever</i>
Total freshmen	4606	100.0	
Total freshmen with history of rheumatic fever	99	2.2	100.0
Total freshmen with rheumatic valvular heart disease	35	0.8	35.3
Total freshmen with history of rheumatic fever on prophylaxis	20		20.2
Number of recur- rences of rheumatic fever while on prophylaxis	0		0.0
Number of recur- rences of rheumatic fever without prophylaxis	19		19.2

TABLE 2
TYPES OF VALVULAR INVOLVEMENT IN FRESHMEN
STUDENTS WITH HISTORY OF RHEUMATIC FEVER

Aortic insufficiency	2
Aortic stenosis	1
Mitral insufficiency	21
Mitral stenosis	1
Mitral insufficiency and stenosis	7
Mitral and aortic insufficiency	1
Mitral insufficiency and stenosis and aortic insufficiency	2
<i>Total</i>	<i>35</i>

per cent incidence found in the present study. There appeared to be a greater incidence in rheumatic heart disease in freshmen students (0.8 per cent) in the North Dakota study when compared with the national study (0.26 per cent). However, the number of freshmen students at the University of North Dakota with rheumatic valvular heart disease has dropped markedly in the last four years.²

This sharp decline in the incidence of rheumatic heart disease during the past four years without a concomitant decline in the number of entering freshmen with a history of rheumatic fever is perhaps the most striking finding in this study. The reason for this is not clear. It is possible, however, that the "natural history" of rheumatic fever is changing with time, genetic make-up of the host, or improved nutritional status of

the population or because of some other factor and that a decreasing incidence of rheumatic valvular disease would occur regardless of therapeutic measures employed to reduce incidence of rheumatic fever or rheumatic heart disease.

Since the sulfonamides were first used against the streptococcus organism in 1936,² there has been a well-documented, growing body of scientific evidence that elimination of the group A hemolytic streptococcus organism from the upper respiratory tract will prevent the development and recurrence of rheumatic fever. The demonstration of the effectiveness of penicillin against this group of organisms in 1943³ provided the practicing physician with a safer agent for control of streptococcus infections. Goerner and associates⁴ demonstrated that penicillin eliminated the beta-hemolytic streptococcus from patients with rheumatic fever. Oral penicillin was tested in 1946 and 1947 by Massell and co-workers⁵ and found to be effective in preventing recurrences of rheumatic fever. Since that time, the clinical evidence showing the effectiveness of penicillin prophylaxis in preventing recurrences of rheumatic fever has been overwhelming (see particularly the studies of Rammelkamp and associates^{6,7,8}).

In spite of this evidence, it is interesting to note that only 20 per cent of patients with a history of rheumatic fever in the present four-year study were on prophylaxis. This is not a particularly low percentage when compared with other studies. Sandridge and associates,¹ in a much larger study of rheumatic fever and rheumatic heart disease among college freshmen during 1956 and 1957, found that only 10.9 per cent of all those students who should have been on continuous prophylaxis at the time they entered college actually were on prophylaxis at the time of the study. In a recent study of freshmen students in Montana colleges in the school year 1960-1961, Rosenberg⁹ found that only 13 per cent of the students who should have been on prophylaxis actually were at the time of entering college.

According to the past medical evidence, all 99 students with a history of rheumatic fever should have been on prophylaxis at the time of entering college. The reason why 80 per cent of them were not on prophylaxis was not a part of the present investigation. However, although a few of those 80 per cent were placed on prophylaxis after the attack of rheumatic fever and discontinued medication of their own accord, the vast majority were never placed on prophylaxis by their family physician. The effectiveness of prophylaxis was re-emphasized in this study,

as there was a history of 19 recurrences in 11 patients not on prophylaxis and no occurrences in patients taking adequate prophylaxis.

SUMMARY

A four-year study of rheumatic fever in freshmen students at the University of North Dakota showed 2.2 per cent of entering freshmen had a history of rheumatic fever. The over-all incidence of rheumatic valvular heart disease in freshmen students during this period was 0.8 per cent; this dropped markedly over the four years of the study. Only 20 per cent of those students with a history of rheumatic fever were on prophylaxis against the group A streptococcus at the time of entering the university. There were 19 recurrences in students with a history of rheumatic fever who were not taking prophylaxis and no recurrences in those who were taking adequate prophylaxis.

The authors wish to thank Miss Ruth Noren and the nursing staff of the Student Health Center of the University of North Dakota for their kind cooperation in assisting in the above investigation.

This paper was read by Dr. Olmstead as part of the Founders Lecture, Indiana Academy of General Practice, French Lick, Indiana, March 7, 1962.

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SAFE AND EFFECTIVE dosage of Dicumarol may have both an upper and a lower limit. In vitro tests in 12 patients given small amounts of the anticoagulant showed a 26 per cent longer prothrombin and 17 per cent longer plasma-thromboplastin time than in untreated controls; other coagulation tests reflected increased coagulability, however. In the same patients, large amounts of Dicumarol increased prothrombin time about 115 per cent in vitro; prolonged clotting, platelet-clumping, and plasma-thromboplastin times; and lowered adhesive index. In vivo coagulation tests in 12 patients given small doses showed slight shortening of platelet survival; high doses greatly lengthened platelet half-life and correspondingly diminished platelet turnover.

E. A. MURPHY and J. F. MUSTARD: Platelet economy during moderate and intensive Dicumarol therapy. *Lancet* 2:960-962, 1961.

Urticaria in Childhood

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The constantly shifting pattern of urticaria and the giant hives of angioneurotic edema are familiar to all. Although the localized edema of urticaria is associated with itching, the non-pitting edema of angioneurotic edema is usually not pruritic.

These diseases occur in about 14 per cent of children.¹ Urticaria is the result of a change in cutaneous capillary function that results in vasodilation and the transudation of plasma.² The basic cause of the disorder is believed to be the release of free histamine. This can occur in a variety of circumstances, such as mild trauma to the skin, sudden exposure to extreme cold, or the combination of circulating antigen with tissue antibody. When a tendency toward urticaria exists, the development of the wheals may be more dependent on factors other than antigen-antibody reactions than on the allergy itself.

It is known that hives develop in some persons whenever vasodilation occurs. Traumatic life situations may be responsible for some forms of chronic urticaria.³ Giant urticaria may be hereditary.²

CLINICAL STUDY

It is the purpose of this paper to present 90 cases of urticaria seen in children at the Quain & Ramstad Clinic between 1949 and 1962. They have been separated into allergic, drug-sensitive, infectious, idiopathic, and chronic groups. The inciting factors, course of the disease, response to therapy, and eventual outcome will be discussed.

It has been suggested that most cases of urticaria in childhood may be a manifestation of an infectious exanthem.⁴

"Allergic" urticaria. "Allergic" urticaria was said to exist when urticaria developed in a child with allergic rhinitis, eczema, or asthma but with no history of preceding infection or drug ingestion or injection. Twelve children, 7 girls and 5 boys, were classified in this group. In 7 children,

no inciting factor was found. Ingestion of cucumbers, peaches, cherries, or peanuts and exposure to a hay mattress directly preceded the disease in 4 children. One child was given an injection of 1-5,000 weed-mold antigen a few hours before the onset of the urticaria, which lasted three days. The average duration of urticaria in these children was three to four days.

Drug urticaria. There were 14 children, 8 boys and 6 girls, who had hives following the ingestion or injection of an antibiotic or chemotherapeutic agent. The lesions occurred from one to eight days after exposure to the agent. Twelve reactions were due to penicillin; one, to a penicillin-sulfonamide mixture; and one, to a sulfonamide. The average duration of the disease was three to seven days.

Infectious urticaria. Twenty-five children were seen with urticaria preceded by an infection. There were 10 boys and 15 girls in this group. Two children had had chickenpox, 1 child had hepatomegaly thought to be caused by hepatitis, 1 child had infectious hepatitis,⁵ 2 children had acute gastroenteritis, 1 child had otitis externa, and 18 children tonsillitis or bronchitis. Hives in these children was present three to four days. Twenty-three of these patients had no history of allergy.

Idiopathic urticaria. Thirty-two children, who had no known major allergies and no contacts with known allergic substances, were classified as having idiopathic hives. In this group, there were 19 boys and 13 girls. Two of these children had giant urticaria. A 6-year-old girl, who had urticaria for one week, had severe rheumatic fever one month later and died with acute fulminating pneumonia. The duration of the disease in this group was one to two weeks.

Chronic urticaria. In 7 children, the disease recurred over periods ranging from two months to five years and was said to be chronic. No specific etiology was found in 4 of these children. One boy is living in a home situation which is threatening to him and to his mother. He also has urticaria in response to exposure to cold. One

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STATISTICAL SUMMARY

	Number	Major allergies present	Duration
Allergic	12	12	3-4 days
Drug	14	4	3-7 days
Infections	25	3	3-4 days
Idiopathic	32	0	1-2 weeks
Chronic	7	2	2 mos.-5 years
Totals	90	21	

other child has urticaria in the winter only. One child had hives which persisted for two months after a penicillin injection.

TREATMENT

All of these children have been treated by a regimen which has included epinephrine, antihistamines, and steroids in selected cases. If there was a primary disease, this received whatever attention was indicated without reference to the urticaria. Because itching stopped and hives disappeared so rapidly in most of these children who received steroids early in the course of the disease, triamcinolone is now given routinely when hives appear, except when contraindicated. Chickenpox and herpes zoster may become fulminating if treated with steroids.

DISCUSSION

In childhood, urticaria is a common response to a number of situations. Its course is usually acute, short, and possibly self-limited. It is usually a benign disease. It may occasionally usher in a severe form of rheumatic fever.⁶ Penicillin caused urticaria in 13 per cent of these children. Twenty-one children (23 per cent) had major allergies, such as eczema, allergic rhinitis, or

asthma. In 2 children, there was a positive allergic family history.

Children with papular urticaria,⁷ which is probably a response to insect bites and mast-cell disease (pigmented urticaria),⁸ were also seen during the period covered by this report but are not included in this study. No cases of urticaria factitia or cases of urticaria due to light sensitivity were seen.

SUMMARY AND CONCLUSIONS

The histories of 90 children with urticaria or angioneurotic edema were studied. Twelve children had "allergic" urticaria; 14 had received an antibiotic or chemotherapeutic agent that had been given for an infectious disease; 25 had urticaria develop during or following infectious illnesses for which no treatment had been offered; 32 children had had no known stimulating contacts; and, finally, 7 children had this disease in a chronic form. In 40 children in this series (44 per cent), the development of urticaria was associated with an infectious disease, usually of the upper respiratory tract.

This paper is dedicated to Dr. L. W. Larson, Bismarck, North Dakota, whose suggestions concerning the care of pediatric patients have always been helpful and appreciated.

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Leonard W. Larson, M.D.

ERNEST J. LARSON, M.D.

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THE FORCES that propel a man into national prominence are many and varied. Most of them are related to time and place. In this respect Dr. Leonard W. Larson was fortunate in both categories.

Dr. Larson's parents came to the fertile and rich land of southern Minnesota in 1880. There they raised their family and prospered, his father being active in the hardware and milling business and later acquiring a drug store. Leonard was born at the turn of the century at Clarkfield, Minnesota.

Dr. Larson's parents, in common with so many other immigrants, were determined to offer their children the advantages of an education that they themselves had been denied, and subsequent history shows that the Larson children were eager and able students. Leonard's older brother received a Ph.D. in chemical engineering and has been with the du Pont company for many years as head of the explosives department. His sister Dora, Mrs. Ray Phillips, and her husband spent forty-one years in the mission fields of Africa, and he has just finished a term as moderator of the Congregational Church of America. All the Phillips' children have Ph.D.'s and one daughter is a pediatrician. So it goes into the third generation. Leonard is only one of an outstanding family.

Among the factors that turned Leonard's

thoughts toward medicine undoubtedly was his close friendship with Dr. Beck, who practiced in Clarkfield for many years. Also I think of the rising stature of the Mayo Clinic, which had already acquired a position of national prominence. Their fine work and opportunities offered by them for study turned many young men and women toward careers in medicine.

After high school at Clarkfield, Leonard went to St. Olaf College at Northfield, Minnesota. Here he had the opportunity of working closely with F. Melius Christiansen, probably the most famous choir and band director in the country at this time. Since his father had been choir director and pianist for the Norwegian Lutheran Church at Clarkfield, Leonard had lived with music. His voice was not good enough to make the choir, but he did become an acceptable baritone horn player and band librarian.

At the University of Minnesota Medical School, which was later to give him an Alumni Outstanding Achievement Award, he concentrated on bacteriology and pathology and graduated Magna Cum Laude in 1922.

Because of specialization in medical school, he decided to do general practice for a time and began his career in Northwood, Iowa, in June 1923. This lasted only one year. "I found out two things," he recalls. "The first is the great difficulty under which many general practitioners work and the second, that I didn't like general practice for myself."

Dr. Larson now returned to the University of

ERNEST J. LARSON is with the DePuy-Sorkness Clinic, Jamestown.

Minnesota for postgraduate studies in pathology and bacteriology. He had been laboratory assistant to Dr. Winfred P. Larson, noted bacteriologist who, along with Dr. E. T. Bell, head of the Department of Pathology, greatly influenced his career. It was Dr. Bell who recommended him for appointment as pathologist at the Quain and Ramstad Clinic at Bismarck, North Dakota.

During his residency in pathology at the University of Minnesota, Dr. Larson met an attractive history student, Miss Ordella Miller, whom he married on October 23, 1923, in Fairmont, Minnesota. They have 2 married daughters and 6 grandchildren.

In 1924, the Larsons set out for Bismarck and found, on the wide open prairie, the well-developed clinic founded by Drs. Quain and Ramstad early in the 1900's. Dr. Larson was the first practicing pathologist in the state, the only other pathologist being at the University at Grand Forks.

The Larsons soon made a place for themselves in Bismarck, and Dr. Larson found time to be active on the school board, in Rotary Club, and in many other local projects.

It was when the depression of the 1930's brought forth the need for many changes in our social and welfare structure that Dr. Larson's talent for medical politics first came to the front. Many bills were introduced in the legislature pertaining to medical care, and soon Dr. Larson found himself the main spokesman for the profession on medical legislation. He was elected secretary of the state association in 1940 and held this position until 1947, when a part-time, paid executive secretary was employed. During this entire period, Dr. Larson had given freely of his time in an effort to guide the legislators along lines that were in the public interest. He was on the committee that helped set up the medical center at Grand Forks and greatly enlarged and improved the two-year medical school at Grand Forks, and he was president of the North Dakota State Medical Association from 1950 to 1951.

Dr. Larson, along with Mary Snyder, executive secretary of the North Dakota Cancer Society, was the main force back of the expansion and development of the North Dakota Chapter of the American Cancer Society, which was to play an important part in the education of the public and the raising of funds for cancer research in North Dakota. For his contribution to cancer control, he received a Gold Medal from the American Cancer Society in 1953.

Dr. Larson was a member of the A.M.A. House of Delegates from 1940 to 1950, representing the

section on pathology and physiology. He was also a member of the Council on Scientific Assembly and chairman of the Correlating Committee on Lay-Sponsored Health Plans, the Commission on Medical Care Plans, the Trustees Committee on Socio-Economic Problems of the profession, and the Committee on Blood. He is one of several who organized the Joint Blood Council, and he served for four years as president of that group.

During the depression years an incident occurred which at the time did not seem important. Lulu B. Evanson, social secretary to the Farmers Union of North Dakota, had been working hard to improve the health situation among the farmers of North Dakota. She stopped Dr. Larson on the street and remarked that the newly appointed Rural Health Committee of the A.M.A. did not have a rural physician on the board. Dr. Larson then reported this complaint to Dr. Olin West, secretary and general manager of the A.M.A. By return mail he found himself appointed to fill the gap, which he did for six years during the 1930's. From 1940 to 1951 he represented the section on pathology and physiology in the House of Delegates and in 1951 was elected to the Board of Trustees.

Dr. Larson by now was deeply involved in many phases of organized medicine that took him away from Bismarck. It was only through the cooperation and assistance of the fellow members of the clinic that he was able to be away from home so much. During the early period, before he had an assistant, he would carry a microscope with him on his travels. Prepared slides or sections of tissue would be mailed to him at his hotel so he could examine the slides there and report to the clinic by phone.

In 1958 he was elected chairman of the Board of Trustees of the A.M.A. In December 1958 came the controversial report from the Commission on Medical Care Plans, of which he was chairman. This has been called the "Larson Report" although it was signed by all 15 members of the Commission and passed by the House of Delegates in June 1959 without a dissenting vote. A fair appraisal of the report would have to say that it has led to a better understanding between local medical societies and those responsible for third-party plans. It also stresses the need for better and cheaper medical care through self-discipline and broader insurance coverage.

Dr. Larson's philosophy of medical care is that of a moderate conservative. He believes the profession has to move with the times and not close its eyes to social changes. He is strongly opposed to government in medicine and especially

opposes such "political solutions" as the administration's social security approach. He feels it will provide medical services for millions who neither need or want them; it will be compulsory; it will be very expensive and will require much higher social security taxes than now contemplated; it will not cover several million needy aged who are not on social security; and, what is most important, it will eventually result in complete socialization of medicine because of the future demands of pressure groups.

Dr. Larson firmly believes that dedication and self-discipline on the part of the profession will put our health care in such a strong and firm position that we will be able to guide the nation's health plans in the direction of the highest public service. The American medical profession

is dedicated to the care of all people, regardless of their ability to pay. The Kerr-Mills law, when implemented in all states, will provide medical care for the needy and near-needy. It should be given a chance to succeed before any legislation is enacted that will tie in the health care of the aged under Social Security.

Dr. Larson, as President of the A.M.A., opposes any extension of government intervention in the practice of medicine. At the same time, he will do everything possible to promote voluntary health insurance and to encourage physicians to provide the best medical care possible at a price their patients can afford to pay. This is the essence of free enterprise, a system which has given the people of the United States the best medical care in the world.

THE PULSE and the ballistocardiogram are not determined by the same aspect of cardiac function and cannot be expected to give comparable results under all conditions. In healthy persons, the ballistocardiographic record decreases with age, while pulse amplitude increases. The discrepancy is caused by (1) the greater effect of age on the part of cardiac function associated with acceleration of the blood, (2) a large error in the pulse masking the effects of age on the heart, and (3) a small error in the ballistocardiogram due to stiffening vessels.

Of the energy provided by the heart, part is lost as friction, part is the kinetic work necessary to propel blood, and the rest is pressure, or potential energy. The pulse is related only to pressure.

Since peripheral resistance is low in youth, the heart's energy goes largely to moving the blood, and pressure changes are small. However, as peripheral resistance increases in aging vessels, an increasingly larger part of cardiac work goes immediately to raising pressure and an increasingly smaller part to creating blood flow. Additional resistance is caused by the peripheral vasoconstriction seeking to maintain blood pressure as the heart weakens. Thus the heart's effort is redistributed so that a larger proportion goes into the initial increase of potential energy, detected as the pulse, and masks the weakness of the heart.

Ballistocardiographic and pulse estimates of the decline in cardiac acceleration function agree if correction is made for redistribution of the heart's work with age and attention is shifted from pulse amplitude to the slope of the advancing wave front. Both estimates show a decline in acceleration function of about 1.5 per cent a year from the maximum.

1. STARR and S. OGAWA: On the aging of the heart; why is it so much more conspicuous in the ballistocardiogram than in the pulse? *Am. J. M. Sc.* 242:399-410, 1961.

Book Reviews . . .

Problems of Blood Pressure in Childhood

ARTHUR J. MOSS, M.D., and FORREST H. ADAMS, M.D., 1962. Springfield, Ill.: Charles C Thomas. 106 pages. Illustrated. \$5.50.

This brief book is valuable because it fulfills a real need. Though blood pressure determination should be a routine part of every complete pediatric physical examination, little has been published in the past describing optimal technique and even the range of normal values for children of all ages and both sexes. This book furnishes that data in readable style.

An introductory review of the history of blood pressure measurement is quite interesting. The techniques of indirect methods of blood pressure measurement, auscultation, flush technique, digital palpation, and oscillometry are considered. The flush method is particularly well described. Data are presented to show that this technique approximates the mean rather than the systolic arterial pressure. Emphasis is rightfully placed on the importance of a properly fitting cuff for blood pressure determination. A nomogram for guidance in selecting the appropriate cuff size for a child of given height and arm circumference should prove most useful.

Direct blood pressure measurement by intra-arterial cannulation is also discussed. The types of apparatus utilized for measuring and recording arterial pressure and the problems encountered in such recording are discussed at length.

This book will be particularly welcomed by pediatricians and cardiologists but will also be useful to all physicians who deal with children.

EUGENIE F. DOYLE, M.D.
New York

Rheumatic Heart Disease

JACQUES B. WALLACH, M.D., EDGAR F. BORGATTA, PH.D., and ALFRED A. ANGRIST, 1962. Springfield, Ill.: Charles C Thomas. 174 pages. Illustrated. \$7.50.

This small volume is not a treatise on rheumatic heart disease, as might be inferred from its title. Instead, it is primarily a statistical analysis of the morphologic cardiac findings in the 509 cases of rheumatic heart disease encountered among 8,689 consecutive autopsies at New York's Queens General Hospital during the years 1936 through 1950. All specimens had been examined by a pathologist and the protocols had been reviewed by another. The authors have searched for correlations between many variables, such as endocarditis and type of valvular lesion, and the presence of thrombi as related to heart weight, and present more than 50 tables. There are no photographs of specimens, and most readers will be disappointed by the deliberate omission of clinical and laboratory information on the cases. Dr. A. A. Angrist, the pathologist who examined the specimens, has contributed an interesting chapter dealing with the simulation of rheumatic lesions by other valve distortions. The final chapter on "Social and Psychological Factors in Autopsy" emphasizes the bias that may occur in autopsy studies. Presumably this chapter and the data analyses are the work of the sociologist member of the group. This book will be of interest to those pathologists, cardiologists, or surgeons who are looking for specific

incidence values for various rheumatic lesions and complications in a large series of autopsied cases. The book has the excellent format that is generally produced by this publisher.

RAY C. ANDERSON, M.D.
Minneapolis

The Compleat Pediatrician: Practical, Diagnostic, Therapeutic, and Preventive Pediatrics

WILBURT C. DAVISON, M.D., and JEANA D. LEVINTHAL, M.D., eighth revised edition, 1961. Durham, N.C.: Duke University Press. 257 sections plus index. \$4.50.

"The Compleat Pediatrician," the eighth edition, is presented in an orderly and concise manner, requiring only moments for references not only to differential diagnostic problems but also to known disease entities.

It is evident that the recent advances and newer terms in the pediatric subspecialties have been embodied throughout. Reference tables, including differential diagnoses of disease and various ancillary findings and studies, are readily accessible and particularly valuable, not only for the pediatrician but also for the medical student, intern, and resident. The sections consist of 11 chapters containing various system and chemically oriented diseases. Especially of note are those pertaining to chapter 3, "Skin, Contagious and Exanthem Conditions," where a concise, descriptive picture of the disease is presented. Chapter 4, the section dealing with neurologic, psychiatric, and eye conditions, is of particular value relative to the broad field of pediatrics and neurology. This section is most up to date, with an inclusion of the rare subacute encephalitides as well as the latest information relative to the diagnosis and treatment of such entities as hypersarhythmia. Other chapters in the book also relate quite well the necessary data that is not easily found in the usual textbooks of pediatrics.

This book has a very attractive, durable, paperback cover which allows it to be kept handy in a drawer for ready reference. The orderly index aides in finding material quickly.

All in all, this book should be valuable to the student of pediatrics as a supplement to his textbook and to the house staff, as well as to the practicing pediatricians.

J. T. JABBOUR, M.D.
Oklahoma City

Management of Emotional Disorders: A Manual for Physicians

A. H. CHAPMAN, M.D., 1962. Philadelphia: J. B. Lippincott. 259 pages. Illustrated. \$8.50.

Physicians who were trained before medical schools began to offer undergraduates more adequate instruction in psychiatry often feel ill-equipped to deal with the estimated third of their patients whose principal problem is psychiatric disturbance. Many of these doctors are, therefore, taking one of the increasing numbers of postgraduate courses in psychiatry, but many others find that distances and limitations in time make such study impractical. These physicians must then turn to textbooks and journal articles for help. All too often, how-

(Continued on page 16A)

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BOOK REVIEWS

(Continued from page 278)

ever, such sources contain jargon beyond the experience of the nonpsychiatrist. What is more, even an understandable textbook may be too old to reflect the remarkable advances in psychiatry of the past five years or so. Physicians need an up-to-date book on the psychiatry of medical practice.

Chapman has given us such a book. Clear, readable (despite a perhaps oversimplified style), accurate, and complete, this work both retains the useful old and introduces the new. Although written with the practicing physician in mind, it has value for the medical student, the intern, and the resident, as well as for the psychiatrist teaching continuation courses. On the one hand, it gives broad orientation in the field of psychiatry with its many confusing complexities; on the other, it offers detailed suggestions and guidance.

Not only the new psychiatric drugs are described, but also modern psychiatric principles, such as the use of psychiatric services in community general hospitals, early discharge from state mental hospitals, ambulatory treatment of mentally ill patients living at home and continuing their jobs, utilization of the family and community resources in therapy, and effective employment of psychiatric consultation. It stresses the value of combining psychiatric and somatic therapies in the treatment of either physical or mental illness.

There are no flights of theoretic fancy here; this book will please the most hard-headed and practical doctor. And it will help him do just what he is in the best position to do—give total medical therapy.

WILLIAM F. SHEELEY, M.D.
Washington, D. C.

Thalassemia: A Survey of Some Aspects

ROBIN M. BANNERMAN, 1961. *New York: Grune & Stratton. 138 pages. Illustrated. \$6.50.*

Comprehensive coverage of the general field of thalassemia is presented in this monograph which should be very helpful to those clinicians who are interested in hematology. Many of the current advances and recent metabolic studies of hemoglobin, together with related disorders, are clearly described. The genetics of thalassemia and its distribution over the world are also discussed.

The contents are written in a very orderly manner and include Historic Aspects, Genetics and Distributions, Clinical Features, Hematology, Heterogeneity of Thalassemia, Hemoglobin Metabolism, Disorders of Hemoglobin Synthesis, Iron and Hemoglobin Metabolism in Thalassemia, and Theories of Pathogenesis, together with very complete reference lists.

The book is very interesting and easy to read and should be of interest to both the specialist and general physician.

EDWARD N. NELSON, M.D.
Minneapolis

Classics of Cardiology

FREDRICK A. WILLIUS, M.D., and THOMAS E. KEYS, 1961. *New York: Dover Publications. 858 pages. Two paperback volumes. Illustrated. \$4.00.*

One of the pioneer American cardiologists and certainly the dean of cardiologists in the Midwest is Dr. Fredrick A. Willius of the Mayo Clinic, Rochester, Minnesota. Throughout his brilliant clinical years, he has evidenced

a deep interest in medical history. In 1941, in conjunction with Mr. Thomas E. Keys, Mayo Clinic librarian, Dr. Willius published a monograph entitled "Cardiac Classics." This volume included the collection of the classic works concerning the heart and circulation and an excellent biographical account of each of the authors concerned. The foreword to these present volumes, written by Dr. Donald C. Balfour, is as valuable and pertinent today as when it was first written.

These are excellent reference works for anyone interested in cardiology. The volumes bring together in a clear, concise manner the classic descriptions of the cardiovascular diseases and make the descriptions live because of the associated biographical sketches. The selections are well chosen, carefully presented, and encompass the great classic works in cardiovascular disease. The 2 volumes are complete, consisting of 52 contributions by a total of 51 authors. The format is excellent, the printing readable, and the illustrations sufficient.

JOHN F. BRIGGS, M.D.
St. Paul

Tumors of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment

MAX CUTLER, M.D., 1962. *Philadelphia: J. B. Lippincott. 482 pages. Illustrated. \$22.50.*

All geriatricians will be happy to see this beautifully illustrated and well-written book by one of the world's experts on the subject. No one can be a geriatrician, especially for women, until he knows well all the diseases which can attack the breast of the elderly woman. There are good bibliographies throughout the book.

Dr. Cutler tells of some families in which breast cancer seems to be hereditary. Particularly good is Chapter 12 on examination of the breast using various techniques. Often much can be told by transilluminating the breast with an ordinary flashlight. The breast can also be studied roentgenographically. Often much can be told from just looking at the breast or from studying discharges from the nipples.

One of the first pages to which many surgeons will turn is page 83 on which Dr. Cutler discusses the question of simple mastectomy combined perhaps with radiotherapy. Today, as we all know, there is much discussion about the advisability in many cases of doing only a simple mastectomy. At first glance, McWhirter's statistics for simple mastectomy seem to be better than those of several surgeons who perform the radical operation. McWhirter, in Edinburgh, reported a 10 per cent increase in 5-year survivals when radical mastectomy was replaced by simple mastectomy plus radiotherapy.

Palliation from radiotherapy is hard to believe in after one reads Harrington's report of radiation, based on some 5,000 cases at the Mayo Clinic. The findings convinced Harrington that x-ray treatment did not make any difference in the final results of the treatment of patients with cancer of the breast. Dr. Clagett's extensive statistics based on the Mayo Clinic experience show clearly that their results with radical mastectomy have been distinctly better than those of McWhirter. McWhirter reported 5-year recoveries in 41.8 per cent, while at the Mayo Clinic the corresponding figure was 64.2 per cent. A similar result was obtained with radical excision in the Dakotas. These figures would seem to dispose of McWhirter's claims.

Dr. George Crile, Jr., is now conducting an interesting

(Continued on page 18A)



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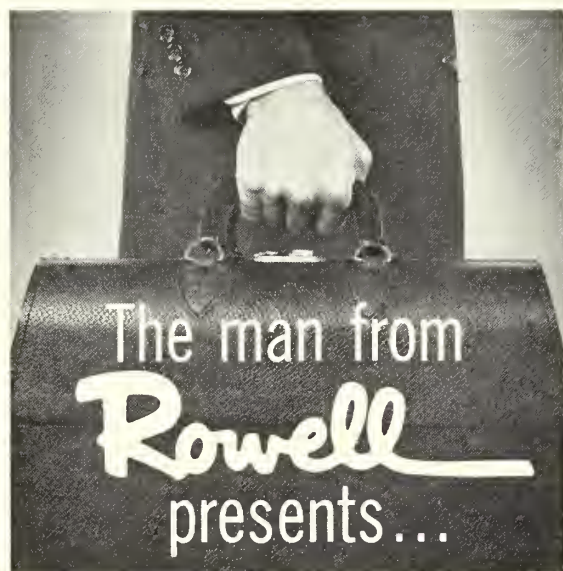
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BOOK REVIEWS

(Continued from page 16A)

bit of research on the use of simple mastectomy, especially in those cases where there are no enlarged glands in the axilla. So far 3- to 6-year results of the simplified treatment have been found to be at least as good as those of the conventional treatment, and the morbidity has been less. Paterson and Russell studied 1,461 cases of breast cancer in an effort to determine the value to postoperative radiotherapy, and they, like Harrington, could not see that it has any effect. Doubtless, x-ray therapy will continue to be used for years, if only so that the patient and the family can be satisfied and, perhaps, so that the family later cannot sue for heavy damages.

Very interesting are the descriptions Dr. Cutler gives of patients with benign and also bizarre tumors of the breast.

For years, this book is likely to be the standard medical reference work on the breast.

WALTER C. ALVAREZ, M.D.
Chicago

Measurements of Exocrine and Endocrine Functions of the Pancreas

F. WILLIAM SUNDERMAN, M.D., and F. WILLIAM SUNDERMAN, JR., M.D., editors, 1961. Philadelphia: J. B. Lippincott. 203 pages. Illustrated. \$11.00.

The edited proceedings of an applied seminar on Measurements of Pancreatic Function in Clinical Medicine held under the auspices of the Association of Clinical Scientists constitutes this book. The purpose of the seminar is to emphasize methodology and yet encompass fundamental chemical considerations and clinical interpretations.

The book is clearly divided into three sections: (1) exocrine function, (2) endocrine function, and (3) fibrocystic disease of the pancreas. Each chapter presents general considerations of the topic and a thorough description of the method for determination of the specific exocrine or endocrine under evaluation. Included in the section of exocrines are the examination of intestinal contents in pancreatic deficiencies and evaluation of pancreatic function in acute and chronic pancreatic disease. The section of endocrine function deals primarily with the problems of insulin assay, insulin antagonist, the significance of glucagon, and the measurement of reducing substances in the urine and ketone bodies in blood.

The collection of articles by the many, well-qualified investigators are brief, clear, and accompanied by a helpful bibliography. The book is of value to clinicians and investigators interested in diseases of the pancreas and is of particular value for those who wish to pursue tests for pancreatic function.

B. J. KENNEDY, M.D.
Minneapolis

Hypertension: Recent Advances

ALBERT M. BREST, M.D., and JOHN H. MOYER, M.D., editors, 1961. Philadelphia: Lea & Febiger. 660 pages. Illustrated. \$12.00.

At the First Hahnemann Symposium on Hypertensive Disease, held in December 1958, it was pointed out that the specific causative mechanisms and definitive therapy of hypertension are controversial. This is also true of the Second Hahnemann Symposium held in Philadelphia in May 1961, the lectures from which are found in this book. The speed of scientific advancement in this area is obvious, however, from the fact that a second symposium was required just two and a half years after the

BOOK REVIEWS

first. The major achievements during the past few years have included newer knowledge of catecholamine metabolism and an improved understanding of the interrelationships between arteriosclerosis and hypertension. In addition, all the presently known facts and theories of the natural history, etiology, and pharmacology of hypertension are reviewed. There are complete discussions on new blood pressure norms in the elderly and interesting comments on the relation between hypertension and the psyche. There are good summaries of the results of new surgical procedures for renal vascular hypertension, the relation of aldosterone to malignant hypertension, and information on the clinical application of catecholamine tests of the urine and plasma are also included.

This book is recommended to the general practitioner, the internist, and any student of hypertension who seeks to be brought abreast of the recent advances and current treatment of hypertensive disease.

EARL HILL, M.D.
Minneapolis

NEW BOOKS RECEIVED

Books and publications received will be listed here periodically, and such mention must be regarded as sufficient return for the courtesy of the sender. Books of special interest to our readers will be reviewed as space permits.

Multiple-Choice Examinations in Medicine. JOHN P. HUBBARD, M.D., and WILLIAM V. CLEMANS, PH.D., 1961. Philadelphia: Lea & Febiger. 186 pages. \$3.75.

Myocardiosis. FERDINAND WUHRMANN, M.D., 1960. Springfield, Ill.: Charles C Thomas. 215 pages. Illustrated. \$10.50.

The Photography of Patients. H. LOU GIBSON, 1960. Springfield, Ill.: Charles C Thomas. 184 pages. Illustrated. \$10.50.

A Physician's Introduction to Electronics: A Laboratory Manual. A. C. MORRIS, JR., 1961. New York: Pergamon Press. 43 pages. Illustrated. \$2.50.

The Physiological Basis of Medical Practice. CHARLES H. BEST and NORMAN B. TAYLOR, editors, 1961. Baltimore: Williams & Wilkins. 1,554 pages. Illustrated. \$16.00.

Quinones in Electron Transport. G. E. W. WOLSTENHOLME and CECILIA M. O'CONNOR, editors, 1961. Boston: Little, Brown & Co. 435 pages. Illustrated. \$11.00.

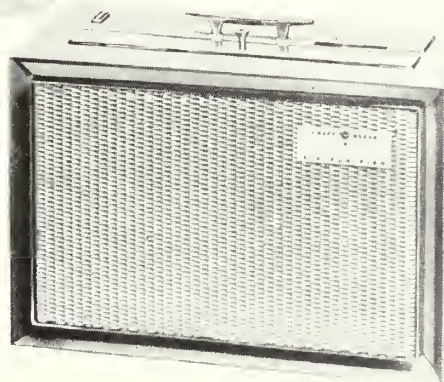
Retirement Villages. ERNEST W. BURGESS, editor, 1961. Ann Arbor: University of Michigan Press. 156 pages. Illustrated. \$3.50.

Sources for Hospital Administrators: Publications and Facilities Serving the Health Administration Field. PAUL WASSERMAN, 1961. Ithaca: Cornell University Press. 60 pages. \$2.00.

Virus Meningo-Encephalitis. G. E. W. WOLSTENHOLME and MARGARET P. CAMERON, editors, 1961. Boston: Little, Brown & Co. 120 pages. Illustrated.

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News Briefs . . .

North Dakota

DR. JON V. EYLANDS, a native of Minot, has joined the Johnson Clinic in Rugby. Dr. Eylands practiced most recently at the Rolla Clinic where he was associated with Dr. Allen R. Neuenschwander. Dr. Neuenschwander bought the Clinic when Dr. Eylands moved to Rugby.

• • • • •

DR. VICTOR FAJAIMO, a urologist, and Dr. LUIS F. ALFUZARRA, a general surgeon, have joined the staff at the Veterans Administration Center in Fargo. Both fled Cuba to practice in the United States.

• • • • •

DR. JAMES R. MORTON, who recently resigned from the Quain and Ramstad Clinic in Bismarck, has joined the staff at the Marysville Medical Clinic, Marysville, California. Dr. Morton received his medical degree from Harvard University Medical School.

• • • • •

THE UNIVERSITY OF NORTH DAKOTA SCHOOL OF MEDICINE has received 3 recent grants. The Louis W. and Maud Hill Family Foundation has given \$75,000 to support a research professorship in cellular metabolism in the department of biochemistry for five years. Wyeth Laboratories gave \$2,000 for the general support of

medical education. The Avalon Foundation in New York City provided \$5,000 for nonrefundable grants to students at the medical school.

The University School of Medicine reports that the number of qualified students applying for admission has increased considerably this year, including 40 from North Dakota. In May, 35 sophomore students will be assigned to hospital clinical clerkships in Fargo, Valley City, Jamestown, Bismarck, Dickinson, Minot, Rugby, and Grand Forks. They will work under preceptors in the hospitals.

Since last September, the school of medicine has participated in the program of Medical Education for National Defense. Dr. T. H. Harwood, Dean of the school of medicine, is coordinator with Dr. John W. Venues, assistant.

Minnesota

DR. ERLING T. HAUGE has been elected president of the staff at Swedish Hospital in Minneapolis. Other officers elected are Dr. J. L. Stennes, president-elect, and Dr. William H. Card, secretary-treasurer.

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DR. GENE R. SVELKOUK has been named chief-of-staff of St. Michael's Hospital at Sauk Centre. Dr. Kent Westley was elected vice-president and Dr. J. C. Grant, secretary. Drs. W. D. Cleaves, Julian F. DuBois, Jr.,

(Continued on page 22A)



Coca-Cola, too, is compatible with a well balanced diet. As a pure, wholesome drink, it provides a bit of quick energy ... brings you back refreshed after work or play. It contributes to good health by providing a pleasurable moment's pause from the pace of a busy day.



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NORTH DAKOTA, SOUTH DAKOTA, AND MONTANA

Series on PSYCHIATRY for the PRACTITIONER

Psychotherapy and the Physician

RICHARD W. ANDERSON, M.D.

Minneapolis

PSYCHOTHERAPY has been defined as the utilization of interviewing by a professional person to relieve or modify symptoms of emotional origin, ameliorate patterns of disturbed behavior, and promote personality growth and development. The effectiveness of psychotherapy has been well known for centuries. Generally recognized as the "art of medicine," it has been taught mainly by the individual case method. Only in recent years have attempts been made to classify and describe the technics which may be effectively used by the nonpsychiatric physician.

Today every physician must, if he is to give comprehensive care to his patients, practice psychotherapy. Treatment of emotional disorders never has been and never will be the sole responsibility of psychiatry. At the present time we have about 10,000 psychiatrists practicing in this country. Approximately 7 per cent of men completing internships elect to enter this field. This figure has remained quite constant over the postwar years and suggests that our supply of psychiatrists will parallel our supply of physicians in all branches of medical practice. At present we need 20,000 psychiatrists, or twice the number now available, to adequately staff

our mental hospitals and mental hygiene clinics and to provide something approaching an adequate amount of specialized private service.

Current studies of our production of physicians as compared with our production of U.S. citizens indicates quite clearly that any modest increase in our supply of doctors is falling far short of our rapidly expanding population. The most conservative of these studies indicates that within fifteen years we must be turning out 2,000 more medical school graduates each year if we are to preserve our current ratio of 132 physicians per 100,000 population. It appears more than probable that, despite courageous leadership and the stimulus given medical education by private, state, and federal funds, we shall have fewer physicians per capita in the coming years.

Thus, it becomes clear that we cannot look forward to the day when all patients with emotional problems can be promptly referred for specialty treatment. Nor can we look forward to a time when the supply of physicians is so ample that each will have what he considers adequate time for the treatment of emotional disorders. If psychiatry is to remain within the medical domain, it is imperative that we develop and utilize techniques which can lead to the most rapid relief of symptoms, leaving for the psychiatrist only

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those patients who must enter mental hospitals and those plainly requiring intensive outpatient psychotherapy.

Patients seek psychotherapy for many reasons. The vast majority do so because of anxiety, depression, or psychophysiologic symptoms. A smaller number of patients come to the physician with the insight that the roots of their problems lie in the area of disturbed interpersonal relationships and with a concurrent desire for personality reorientation. Such patients do not constitute a burden for the nonpsychiatric physician; they seek psychiatric referral through their physicians or refer themselves to psychiatrists or psychiatric clinics. It is the patient who seeks only symptomatic relief who repeatedly returns to his physician for care and often resists psychiatric referral.

No one is yet certain whether it is lack of time or the conviction that a profound knowledge of psychodynamics is necessary to practice psychotherapy which prevents medical practitioners from entering into a psychotherapeutic relationship with patients. It is, however, repeatedly demonstrated in teaching clinics that many medical students with understandably limited experience in dealing with patients can, under supervision, consistently provide therapeutic contacts which result in relief of patients' symptoms.

That there is a desire on the part of all physicians for means to produce rapid relief of emotional symptoms is best illustrated today in the phenomenal sale of tranquilizing drugs. About 1.25 billion meprobamate tablets are dispensed annually in this country. The extensive use of drugs is cited only to indicate the magnitude of the treatment problem, since drugs are, at best, an adjuvant to psychotherapy. Their extensive use does tend to support previous estimates made by many medical practitioners that 40 per cent of patients consulting doctors do so because of symptoms of emotional origin. All of us are aware of how profoundly some of these drugs can influence the physiology, behavior, and subjective state of the patient. Nevertheless, many physicians feel, each time they write a prescription for one of these drugs, that it will not do what the doctor many times can do, namely provide more permanent relief through proper expression of feeling, through reorientation regarding a personal problem, or through the subtle interchange that has become known as the doctor-patient relationship. What drugs do accomplish is a reduction of symptoms so that the physician can effectively explore and deal with the emotional stresses existing in the patient.

The time required for psychotherapy constitutes a problem for all of us and is usually one of the first arguments advanced by busy general practitioners who claim that they cannot "do" psychotherapy. All are aware that each contact with a patient is psychotherapeutic in one way or another. It has often been shown that recognition of the patient's emotional problems and needs, establishment of reasonable goals for psychotherapy, and choice of the proper psychotherapeutic techniques will save the physician's time in dealing with a given patient and will at the same time increase the physician's effectiveness.

Because of the conviction that general physicians and nonpsychiatric specialists must do the greater portion of the psychotherapy in medical practice, the Psychiatric Outpatient Clinic of the University of Minnesota Hospitals has, during the past ten years, assigned medical students in their clinical years to the majority of the patients attending the clinic. In this setting the student functions as the patient's physician, undertaking various psychotherapeutic maneuvers arrived at in consultation with the psychiatrist, social worker, and clinical psychologist, as well as with the help of his student colleagues. We feel that placing the student in the role of the therapist allows him to have a personal acquaintance with the effectiveness of psychotherapeutic measures. We hope that some conviction that he himself can effectively and successfully provide therapeutic aid will carry over in his medical practice. Informal contacts with many of these students after some years of practice have revealed that this is often the case. A physician who is convinced that he can help a patient through interview is less likely to use lack of time or lack of sufficient skill as a rationalization for not attempting any planned psychotherapy with a patient.

In order to set realistic goals and not involve students in situations where expectations might exceed all reasonable possibility of accomplishment, we emphasize a thorough diagnostic study followed by a discussion of desirable psychotherapeutic goals in each case. These are defined in terms of improved life function or symptomatic relief. It becomes obvious that it is one matter to treat a patient with a good ego and a tension headache and quite another to attempt to relieve the somatic symptoms of a patient adjusting to life on the basis of chronic "pseudoneurotic" schizophrenic reaction.

Therapy by a medical student provided relief in the case of a woman in her early 30s who was referred to the psychiatry clinic from the neu-

rology clinic where she had been studied for headaches. No neurologic illness was found, and several monthly visits to a headache clinic operated by the neurologic service failed to provide her with relief. Her history indicated that she was seething with rage directed toward a husband who was in the habit of leaving her alone with several small children while he pursued a culturally rewarded pattern of spending every night with male friends in the local tavern. In the therapeutic situation, she was commended for the effective ventilation of her anger and her headaches soon disappeared. Although it may sound disarmingly simple, we regard the effective expression of her justifiable rage as one of the most important of the therapeutic maneuvers employed by the nonpsychiatric physician and agree with Rado¹ when he says, "The release of repressed rage is a decompressive procedure comparable to the opening of a blind abscess. To release the repressed rage one must first locate and revive it in the memory context of the life experience that provoked it. Furthermore, to be successful, the release must retrieve the patient's lost pride. This effect can only be obtained if the patient feels that the physician approves of his released rage."

In the previous case, the release of rage was effective, but it would not have been if one were dealing with a patient having a diagnosis of pseudoneurotic schizophrenia. A 40-year-old woman appeared at our clinic with vague pains in the upper abdomen, chest, and left arm. A review of her history indicated that somatic symptomatology of one sort or another had protected her from entering actively into life's struggle for a period in excess of twenty-five years. Her pains served to cement a dependent bond to a solicitous husband. Any expression of rage in this patient would have upset her characteristic method of getting along in life and would probably result in a rapid deterioration of her adjustment, possibly leading to hospitalization. Her treatment instead was aimed at more effective utilization of the dependency relationship with her husband, and her symptoms were partially relieved with drugs. Alteration of a lifelong pattern of schizoid adaptation is as difficult and hazardous for the medical student or general physician as it is for the psychiatrist. Awareness of this fact makes it possible to set realistic goals and avoid therapeutic pitfalls. When somatic symptoms form the cornerstone of a lifelong method of adjustment, a wise physician will not expect the patient to become free of symptoms.

These two examples, in which opposite techniques were used, serve to illustrate the importance of

diagnosis and goal-setting before undertaking psychotherapy. The goals chosen depend upon the ego strength of the patient, the extensiveness of his psychopathology, the patient's relationship with the members of his family, and the chronicity of his illness.

Just as diagnosis and goal-setting must precede therapy, they also must precede a discussion of therapeutic techniques, since the latter seem at first glance to be disarmingly simple. There are many schools of psychotherapy, each claiming success. Students of psychotherapy have suggested that the experts of each school differ much less from one another than do the schools themselves. The best psychotherapists seem to be people possessed of extraordinary interest in their fellow human beings, a broad view of the culture and of the group the patient represents, and a capacity for utilizing proper psychotherapeutic techniques, regardless of theoretic orientation. Despite the diversity of theoretic backgrounds, all psychotherapies can be broken down into several rather simple elements which will now be outlined.

The first of these is "suggestion." Hypnosis makes extensive use of this measure but is not the only suggestive technique which may be employed by the physician. The extensive use of drugs has led to research which has made us increasingly aware of the placebo effect of any drug. It is doubtful that a prescription is ever handed to a patient without at least an implied suggestion that the medicine will make him feel better. Symptoms of all sorts may be relieved in roughly a third of all patients by placebos. Thus we must expect that a tranquilizing drug, for example, to be considered effective to any degree, must clearly demonstrate its superiority over the powerful placebo. This nonspecific effect permeates all aspects of medical practice. The fact that the patient comes to the physician's office or to a clinic and is assured that a physician will pay attention to his problem constitutes in and of itself powerful medicine. This is illustrated in a paper by Ginsburg² in which a follow-up study was done on patients who had previously attended a psychiatric clinic. It was discovered that most patients who attended 5 times or more later replied that they had been helped by their visits to the clinic. When attention was paid to the training of a person interviewing the patient, the findings raised some doubts about the specificity of psychotherapy. Dr. Ginsburg's results indicated that it was of very little importance, in relation to the patient's having reported that he had received help, whether he had been seen by a well-trained psychiatrist or a medical stu-

dent working under supervision. It was more important that the person interviewing the patient, regardless of training, had been able to establish sufficient rapport to make it possible for the patient to return to the clinic for more than 5 visits. Correspondingly, patients who dropped out before having visited the clinic 3 or 4 times almost invariably reported that they had not been helped. Here again there was no sharp division in terms of the training of the therapist. Thus it would appear that what each of us brings to psychotherapy is his own human interest and capacity to allow another person to express his attitudes and feelings. Sophistication, training, capacity to promote insight, and theoretic bias would appear, on the basis of this study, to be far less important. Such a study also indicates the function of a suggestive effect, namely that attendance at a clinic on several occasions represents to the patient a definite source of help. Suggestion exists in every relationship between a physician and a patient. Its effectiveness should never be underestimated, whether this comes by way of prescribing a drug or through sympathetic attention to the patient's problem.

The second technic used by all physicians can best be summed up in the words "emotional relief." The Freudian principle of catharsis remains a cardinal one in all forms of therapy. Catharsis occurs in nonpsychiatric as well as psychiatric settings; we are all aware of the therapeutic effect of relating an incident which angers us to a wife or a sympathetic friend. In a psychiatric setting, however, this relief attains a position of greater prominence, since the therapist is an authority who can indicate that the rage, grief, anger, or fear the patient expresses is appropriate to the situation under discussion. The acceptance and definition of the emotion occurring within the interview provide a powerful method of relieving the patient. Our students are able to do this to varying degrees. On one occasion we discovered a student who could not allow a middle-aged woman to weep. Brief investigation of that student's problems revealed that he was currently suffering with a mother undergoing an involutional depression, causing personal feelings about expression of grief that made it difficult for him to facilitate this for his patient.

Even without special technics for facilitation or authoritative basis for justification of the expression of emotion, the permission to tell one's story is eagerly sought and generally beneficial for patients. Some years ago in New York City, a group of people practiced a profession of

"listening." These "therapists" had no professional background whatsoever. They were chosen for their rather distinguished and sympathetic appearance and functioned by having a client enter the office, sitting in complete silence for one hour while the client discussed whatever he chose, and then collecting the fee and allowing the client to disappear and return again if he wished. Since these were nonprofessional people, an effort was made to legally restrain them from practicing medicine. The listener's case was won in the courts when it was demonstrated that since they were not saying anything, they were not performing any kind of psychotherapy. However, nothing could be further from the truth. The ability to tell one's story to a noncritical authority often provides marked relief to patients and is the most important aspect of the psychiatric interview. The ability to listen without interrupting another person is difficult for most of us and is a point that we stress in the learning experience of our students. The eagerness to obtain a precise chronologic history must be temporarily replaced by a certain amount of ease in allowing the patient to tell his story in his own way. There is some evidence to suggest, as does Deutch in his "associative anamnesis" method, that such listening allows a physician to obtain a more meaningful history with no additional expenditure of time. The principal advantage is that the history taking, in and of itself, becomes therapeutic because of the inherent benefits of catharsis.

"Manipulation" is the third psychotherapeutic technic used by every physician. When a physician hospitalizes a patient suffering from peptic ulcer, the patient enters a situation where the physician has the best possible chance of meeting the patient's dependency needs. He is "nursed," frequently fed on a soft, bland diet, bathed, toileted if necessary, and catered to, and he receives the solicitous support of hospital personnel, the physician, and his relatives. The change in environment from home to hospital is a medical manipulation geared to a dependency need and results in sufficient gratification to relieve the patient's psychophysiologic disturbance. We all use manipulation daily in medical practice, not only in the hospitalization of patients but in giving certain kinds of advice, such as suggestions pertaining to an alteration in marital interaction, or parent-child relationships. Interviews with family members often change the most important portion of the patient's environment. Manipulation may be carried as far as direct giving of advice. Psychoanalytic schools of therapy generally discourage

such practices, although these schools do not always allow patients complete self-determination. Engagement, marriage, divorce, and other important changes in interpersonal relationships are often forbidden during the course of the psychoanalytic therapies. A physician who believes he is right about a manipulative measure can carry it out with therapeutic benefit to the patient, provided the advice given is within the scope of the patient's current ability to function.

There is a second kind of manipulation, however, that is more subtle. This is manipulation of the doctor-patient relationship and can best be illustrated by another brief clinical account. A doctor once told of his experience in a small town where he was the only physician. Having seen Mrs. Jones on one occasion because of vague somatic complaints, he soon found that she was calling him to reiterate these complaints almost every evening. He was at first annoyed and later angered by her phone calls but saw no way of dealing with them until he came upon the idea of scheduling Mrs. Jones one hour per week in his office to express her complaints. The advantages of doing this in the office over those provided by a telephone communication were evident. First, it was done when the physician had time to really listen; second, he received a fee for his professional performance. As Mrs. Jones was able to achieve some emotional relief in response to ventilation and some of the physician's suggestions, he undertook another kind of manipulation. This consisted of spacing the interviews farther apart, first to every two weeks and thence to every month as soon as both he and the patient agreed that such a move would be acceptable. Incidentally, the phone calls diminished and finally ceased as Mrs. Jones received meaningful treatment, and the physician came to realize that he could work effectively with a neurotic patient. He had accepted a dependent relationship within a context that he himself could handle professionally, then he gradually diluted this relationship by means of spacing his interviews. He found that he was happier in this therapeutic process and that Mrs. Jones attained some symptomatic benefit. This kind of manipulation is a regular feature of all psychotherapies, whether they be carried out by psychiatrists or nonpsychiatric physicians.

A fourth psychotherapeutic technique consists of "clarification." Here we are moving closer to the ground that is considered by most physicians to be the particular domain of the psychiatrist, and it is important that we distinguish between an explanation of conscious motivation as opposed to unconscious motivation, to be discussed

later. Clarification consists merely of pointing out to the patient his previous statements about his motives for a particular bit of maladaptive behavior. For example, a patient who chronically comes late to the interview and who reports that he is late to work and in his earlier years was late to school might have this chronic lateness pointed out to him without any further inference being made. The demonstration of the occurrence of pathologic behavior, in this case tardiness, in a number of different situations may then lead the patient to make some inferences about his own behavior. This can lead to effective modification of behavior in some instances and is quite different from an interpretation in which one would say to the patient, "Your chronic lateness in the interview, at work, and at school is an indication of a great deal of passive resistance toward authority figures and indicates previous difficulty with your father."

A simple restatement of things that the patient fears or is worried about often serves to clear matters up in a very striking fashion. This method is completely appropriate for the non-psychiatric physician, since a confrontation or restatement deals only with conscious motivation. When we begin to deal with inferences in regard to unconscious motivation, we definitely enter ground that should be left to the trained psychotherapist.

Interpretation, or the explanation of unconscious motivation, is the fifth of the psychotherapeutic techniques. The attainment of insight by such means was previously regarded as being therapeutic in itself, although psychiatrists since Freud have come to realize that the insight is only the first step in a long process of "working through" which may result in a definite modification of patterns of behavior. In evolving interpretations, use is made not only of the previous life experience of the patient but of fantasy and dream material which is generally outside the realm of competence of most nonpsychiatric physicians. It is, therefore, safe to state that the use of fantasy and dream material and the search for deeper inferences about the import of these have little or no place in the psychotherapy of general practice.

Patients are more resilient psychologically than we often realize but may be significantly damaged by poorly thought out interpretations. These we continually advise our students against. We offer them in the therapeutic situation only when they are carefully considered and well documented by material the patient has previously given and when the patient shows strength and readiness for such insight.

So far as symptomatic relief is concerned, the first 4 methods, suggestion, emotional relief, manipulation, and clarification, are of the greatest importance. Interpretation is of value principally for those patients who seek therapy on an aspiring level—for example, the psychiatrist in training or the writer who wishes to become more productive. Most patients seek therapy only for relief of symptoms and, after receiving brief supportive therapy, can again function in life without the help of a parent figure.

Patients contacting the physician for the relief of symptoms come into therapy expecting short-term procedures. Supportive therapies and the use of drugs are the most characteristic methods for meeting this need of the patient. The patient operating on this level feels that he can get along if he occasionally has the opportunity to discuss his problems with a kind, supposedly omniscient, or at least understanding, professional person. At these levels, the ability to relate to the patient and to communicate with him in his own language, thereby allowing him to express his feelings freely, is our most potent therapy. The first 4 techniques—suggestion, emotional relief, manipulation, and clarification—will serve as useful measures for the majority of patients with emotional problems.

The nonpsychiatric physician is prepared to undertake psychotherapy once he has made a diagnosis and has determined appropriate goals of treatment for patients with dependency problems, patients with neurotic symptoms, or those with psychophysiological disorders. In the main, these do not require deep or sophisticated interpretation in order to achieve considerable symptomatic relief. Patients without definite symptoms or excessive suffering who aspire to a higher level of integration are best referred for psychiatric evaluation. This is also true of those obviously too ill to continue to function, despite the physician's psychotherapeutic assistance.

The majority of patients with emotional problems are suitable candidates for the therapeutic

technics which can be employed by the general physician. Branch and Ely,³ in speaking of the problem of ambulant psychotherapy, have quoted Knight who suggests that there are three elements of successful therapy—"support, rapport and import. More recently, it appears that while import (or insight) continues to be listed as desirable and important, more and more attention is paid to support and rapport. . . . There is more emphasis on the relationship between the therapist and the patient. . . . A successful and helpful relationship appears to depend upon the personal security of the therapist and the degree to which he can establish adequate communication with his patients. These therefore should be the foci of the teaching process."

The ability to relate effectively to a patient has been the focus of the teaching process in our psychiatric clinic at the University of Minnesota for many years. We find that the techniques discussed above can be taught to most medical students in a clinical context without great difficulty. Former students having experienced that they themselves possess some competence as therapists report that they have undertaken systematic psychotherapy in their medical practices. An account of the techniques employed by medical students seems appropriate to a discussion for nonpsychiatric physicians who will use these techniques with still greater competence, since they are operating from a base which includes much broader personal and clinical experience. All physicians carry out psychotherapy whether or not they regard it as such. Attention paid to the techniques used will result in greater satisfaction for the physician and benefit for the patient.

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Functional Electrical Stimulation for Ambulation in Hemiplegia

JOHN H. MOE, M.D., and HERBERT W. POST, B.S.

Minneapolis

THIS IS A PRELIMINARY REPORT on the use of a lightweight, transistorized electronic muscle stimulator in correcting the drop-foot gait of patients with hemiplegia.

In hemiplegia following a cerebral accident, functional recovery frequently progresses sufficiently to permit the patient to walk with satisfactory function of hip and knee. Most often there is, however, a residual paralysis in the dorsiflexion of the foot. The "drop-foot" brace which usually is prescribed permits walking with additional security and ease. Nevertheless, the disadvantages of bracing the foot are recognized, both cosmetically and economically. They include wear and tear of brace and clothing and the need for periodic replacement of the brace.

The use of a painless, portable, electric stimulator which would reactivate the paralyzed muscles and eliminate the "drop-foot" brace obviously would be of great advantage.

It is the purpose of this report to describe such a stimulator and how it permits the patient to walk in a relatively normal manner without the use of a brace.

Electric stimulation of the muscle is a valuable form of therapy in the treatment of strains, sprains, dislocations, and other trauma of the muscle and skeletal system. It often is prescribed for various lesions of the nervous system to maintain the muscle in as normal a state as possible. The objective of the treatment is to improve circulation in vascular and lymphatic channels and to retard atrophy of the muscle. An appropriate type of current applied to the muscles will assist in removing the exudates within the tissues. This electric massage is physiologic in type; it is impossible to produce it by hand.

When a muscle is not able to function in a

normal manner it atrophies. This deterioration affects the connective tissue as well as the muscle fiber. Prolonged denervation of a muscle results in a replacement of its fibers with fibrous tissue, with resultant loss in elasticity. This may hamper the normal use of the muscle seriously when re-innervation occurs.

The response of skeletal muscle to electric stimulation may be studied by application of a current to the skin over the point of entrance of the nerve into the muscle of the belly—that is, the motor point.

FARADIC CURRENT STIMULATION

This form of therapy employs the electric outflow from the secondary of an inductance coil. Its most important property is that it has a sharp spike with a duration of .001 second on break of current. It is this duration that lends usefulness to faradic current in electrodiagnosis. Normal muscle and muscle paralyzed as a result of an upper motor neuron lesion have an average maximal time requirement for stimulation (chronaxie) of .001 second. They will contract if faradic current of adequate intensity is applied. If denervation is present, as in lower motor neuron lesions, the chronaxie is increased. The faradic current's effective duration then will be too short to produce movement. Faradic stimulation thus can be of value for the gross detection of denervation. The current, however, is painful even in moderate intensity. Patients find it unpleasant.

GALVANIC CURRENT STIMULATION

This is a direct current of known polarity with which stimulation may be obtained in a physiologic manner through the negative electrode. In galvanic testing, the most informative observation from direct stimulation of the muscle is the quality of muscle contraction. Normal muscle contracts rapidly and sharply. Denervated muscle responds with a relatively slow contraction, a slower relaxation, and tendency for contrac-

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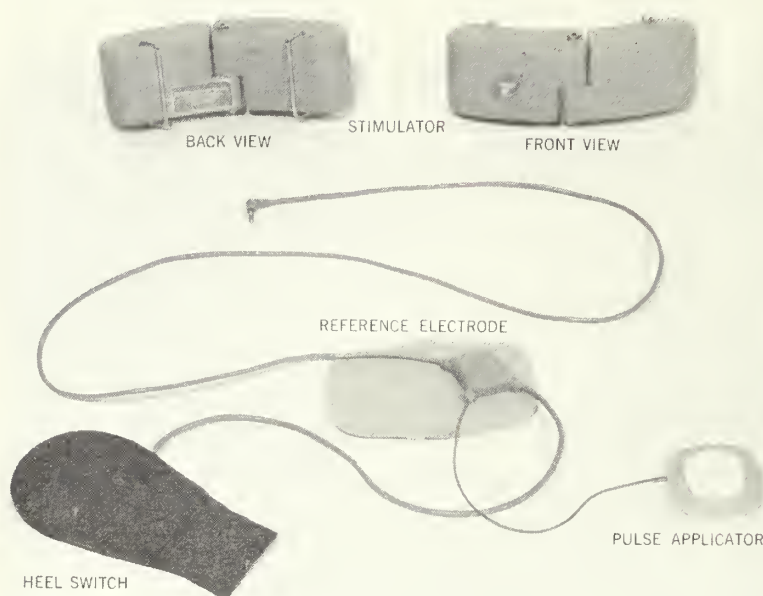


Fig. 1. The complete stimulator unit, showing front and back view

tions to spread to contiguous fibers. The result is a sluggishly spreading, vermicular motion. Studies of the effects of galvanic electrical stimulation for denervated muscles indicate that it is helpful but that it will not prevent completely the effects of denervation. The best results have been obtained with brief periods of stimulation done at least daily. Long periods of galvanic stimulation have been known to cause an erythema and necrosis of the tissue.

The muscle stimulator* used in this study (figure 1) has a current that is nongalvanic, non-faradic, and nonsinusoidal. It generates a one-directional, negative-going, modified, square wave pulse, rated at 10 milliamperes with an intensity adjustable from 20 to 80 volts. Frequency is fixed at 58 cycles per second, and the chronaxie is 150 microseconds. The stimulator develops this current without heat, no matter what intensity is used. Sharp peak voltages are clipped to eliminate sensations of burning.

DESCRIPTION OF THE APPARATUS

The portable transistorized stimulator, worn on the belt (figure 2), weighs less than 7 oz. One electrode supplies the muscle-activating pulse over the selected dorsiflexor (figure 3), while another, slightly larger electrode placed over the gastrocnemius area completes the circuit (figure

4). The electrodes are held in place with an elastic cuff. They are kept moist for as long as eighteen hours with a nonirritating electroconductive wetting agent. The electrodes are disposable and are replaced at intervals for a few cents.

A switch placed under the heel inside the patient's shoe provides an automatic interruption of the muscle-activating pulse which is applied to the dorsiflexor. When pressure on the heel is relieved, as between steps in normal walking, the delivered pulse causes dorsiflexion of the foot



Fig. 2. The stimulator worn on the belt. Wire passes down trouser leg to the electrodes.

*Manufactured by Theratron Corporation, St. Paul.

to a right angle or slightly above a right angle (figure 5). When weight is applied to the heel, the stimulation to the dorsiflexor is interrupted, permitting relaxation of the muscle and completion of the walk cycle. This relaxation can be demonstrated if the unit is unplugged at the belt, with the foot held off the ground (figure 6). An intensity control of the stimulator permits the patient to adjust the pulse signal according to individual requirements. The fine wires from the

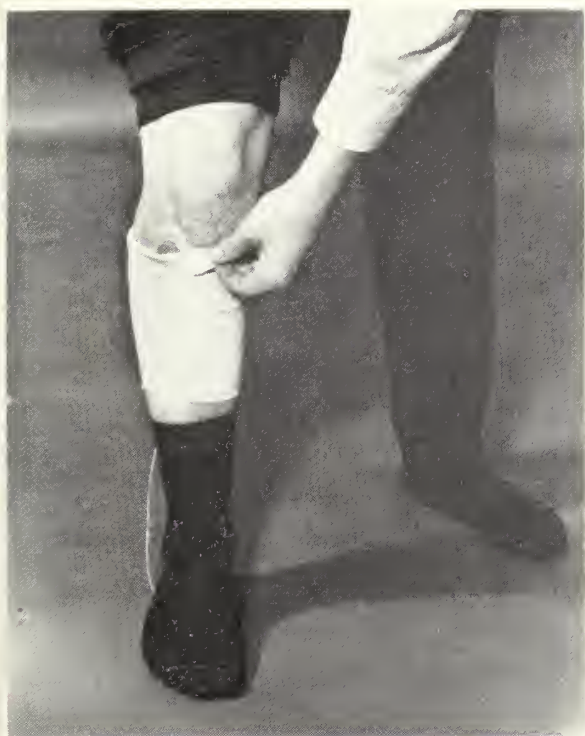


Fig. 3. The pulse-activating electrode placed over the motor point of the selected dorsiflexor—in this case, the tibialis anticus

unit on the belt to the electrodes are hidden within the trouser leg or dress of the patient.

CASE REPORTS

The following case histories illustrate the use of electronic muscle stimulation in treatment of patients with hemiplegia.

Case 1. D. K., a 43-year-old woman suffered a cerebrovascular accident thirteen years before, following a surgical procedure. Hemiplegia on the right side resulted. She had made progress by wearing a single, upright, drop-foot brace with an extended valgus T-strap attached to her shoe. She walked insecurely, with considerable imbalance, and required a cane. She climbed stairs only by the use of a helping rail and with a single-step ascent. There had been no improvement in the past several years. The upper part of the right extremity was moderately involved, and there was some speech difficulty.

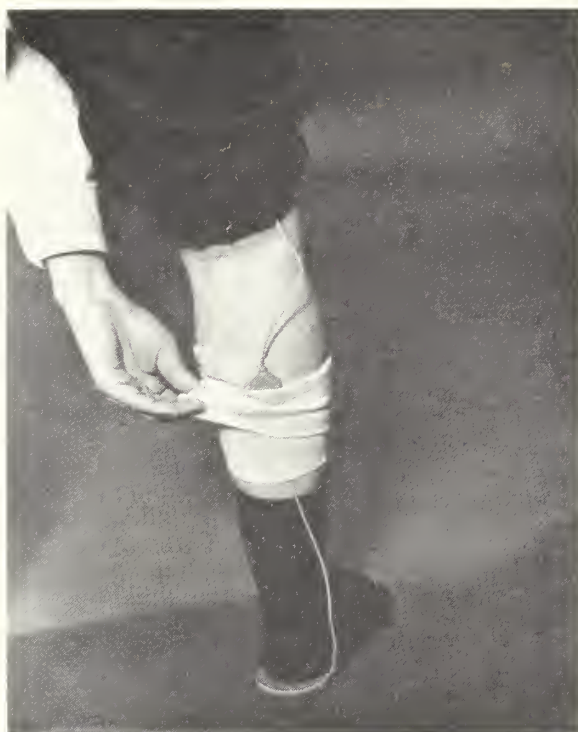


Fig. 4. The reference electrode in place over the gastrocnemius area



Fig. 5. The degree of dorsiflexion obtained with the stimulator in the "on" position

The electronic muscle stimulator first was used in April 1961. At this time she could walk with a marked drop-foot gait without the use of a brace. However, insecurity and imbalance persisted, and she went up and



Fig. 6. The foot in relaxed plantar-flexed position

down stairs slowly and with the help of the rail. She used a cane for additional support at all times. When the stimulation was applied, the anterior tibial response was overactive in relation to the peroneal muscle response, resulting in dorsiflexion into a strong varus position.

It was felt that this could be corrected surgically by transferring the tibialis anticus insertion into the middle cuneiform of the foot. This procedure was carried out on May 9, 1961. A postoperative cast was used for the dual purpose of protecting the tendon transfer and of stretching a somewhat tight tendo achillis.

The cast was removed seven weeks later. Electronic muscle stimulation was reinstituted. The results were gratifying immediately in that the patient's foot now came up into a neutral dorsiflexed position during her walking.

She can, at the present time, walk for several blocks without undue fatigue. She can walk up and down stairs in proper sequence, placing one foot in front of the other in a normal fashion. She walks with scarcely a limp and has no need for a cane or for holding onto a railing or any other object to steady herself.

It also is noteworthy that thirty-four days after the electronic muscle stimulation was reinstituted after surgery, the patient reported a tingling sensation in her affected foot. Some days later, a voluntary movement of her toes was possible, and, after another two weeks, she could move her foot at will in dorsiflexion.

At the time of this report, she has shown further improvement in dorsiflexion. Because of the degree of concentration required, however, she still walks much better with the use of the electronic muscle stimulator.

Case 2. G. K., a 45-year-old man, suffered a cerebrovascular accident from a thrombosis five years before. It left him with hemiplegia on the right side. During the following five years, he was able to walk by wearing a

double-bar drop-foot brace. With this he walked securely, but he fatigued quickly. There also was moderate atrophy of the anterior muscles of the leg on the afflicted side.

When electronic muscle stimulation first was instituted in May 1961, the dorsiflexor response was weak and inconsistent. It was believed that this was due to stretch reflex spasm of the stronger plantar flexors. Daily administering of stimulation to the dorsiflexors for a two-week period brought about a consistent and functional straight lift.

This patient also has shown progressive improvement in walking. He can now walk for greater distances without undue fatigue, and he can move his foot voluntarily in dorsiflexion with minimal effort. There also has been hypertrophy of the dorsiflexors, making his legs of equal size. It also is noteworthy that he is able to walk for sustained periods without the electronic muscle stimulator and without displaying the previous equinovarus toe drag. He is presently wearing the stimulator on the average of ten hours per day.

Case 3. L. F., a 33-year-old man, experienced a cerebrovascular accident in September 1957, from an embolism. Hemiplegia on the left side resulted. During the four years after the accident, he made moderate progress by wearing a double-bar drop-foot brace. He walked securely but fatigued easily. Much of this fatigue was due apparently to his walking with a slightly flexed knee, a pattern which still exists, but to a lesser degree.

His chief complaint during these years was that his leg felt cold. This interfered with his going to sleep unless he first warmed it. Beginning in May 1961, the electronic stimulator was applied for periods which progressed from one-half hour to ten hours daily.

At the time of this report, his gait is much improved and he can walk for far greater distances without fatigue. He claims that when wearing the stimulator his walk feels more natural and requires less concentration. Also noteworthy are traces of voluntary muscle action and the disappearance of the sensation of coolness in his leg. We believe that this is due to better circulation as a result of the stimulation of the muscles.

Similar results have been observed in a number of other patient in this test program.

SUMMARY

This preliminary report presents the effects of controlled electronic stimulation of the muscles on a group of patients with hemiplegia. Those chosen for this test had been suffering for at least four years and their recovery, if any, was at a standstill.

Although the stimulator initially was intended to be evaluated as an electrophysiologic brace, its therapeutic value in bringing back active function of muscles and improved circulation was demonstrated clearly. The patients found this mode of stimulation painless, and they were able to wear the stimulator for long periods without evidence of adverse side effects. It would appear, therefore, that other patients with hemiplegia could expect similar improvement through this type of treatment.

Relative Hypoglycemia

A Clinical Review of 350 Cases

MARTIN S. BUEHLER, M.D.

Dallas

THIS IS A CLINICAL REVIEW of a common condition which is frequently missed or misdiagnosed. It is sometimes called functional hyperinsulinism, which is a misnomer since there is no evidence of any excessive secretion of insulin; as a matter of fact, in a number of patients studied, the circulating blood insulin was entirely within normal limits. The condition is also known as essential or functional hypoglycemia, although I dislike those adjectives because they explain absolutely nothing. I also dislike the word hypoglycemia because it implies that we are dealing with an absolute drop in the blood sugar, which is not the case. However, since we seem unable to eliminate the word hypoglycemia from the literature, I have decided to call this condition relative hypoglycemia, which I hope will explain more adequately what I am trying to describe, that is, a failure of the blood sugar to rise to normal levels after CHO ingestion.

This condition has been described for some ten years or more by various authors, but there is still a great deal of confusion about it in the medical mind. Certainly, by the number of cases that I have been able to collect over a relatively short period, this condition must be extremely common; it is very important as well, inasmuch as most of these cases are misdiagnosed, often as neuroses, and many patients have even been referred for psychiatric therapy. All of this seems quite tragic to me, since the vast majority of them can be rapidly cured of their symptoms or completely kept under control by correct therapy. Space will not permit a complete and adequate description, but I will attempt to cover as much as possible.

SYMPTOMATOLOGY

For a number of years, it has been obvious to some internists and neurosurgeons that they are seeing a large number of patients with neurologic syndromes and deficits suggestive of lesions

of the central nervous system in whom, nevertheless, diagnostic studies yield perfectly normal results. These patients have headaches, frequently intractable, various muscle group deficits or even paralyses, and mental symptoms suggestive of cerebral atrophy or arteriosclerosis, incongruously, most common in younger patients. I will not go into the neurologic muscle group problems, inasmuch as a paper on this is being written by one of our neurologic surgeons. However, I would like to emphasize the importance of looking for relative hypoglycemia in those cases where other studies are within normal limits. The glucose tolerance curves shown in figures 1 through 3 represent the 3 main types seen with this condition.

The first main type is by far the most common and is usually found in persons complaining of headaches, either generalized or occipital, malaise, nervousness, and the like. These patients will frequently state that they feel their mental acuity is less than their normal and will say "I cannot remember what I walked into the next room to pick up." Persons well trained in their field will come in complaining of the fact that they are unable to "use my mind as clearly as is usual for me." It is quite common for patients with any of the 3 types of curve to complain of nervousness, irritability, occasionally insomnia, and a sense of fatigue or malaise, sometimes very pronounced. Inasmuch as almost 100 per cent of them have been treated with sedatives or tranquilizers by myself or by others, with little or no effect, it is obvious that this treatment alone is quite insufficient. In those who complain of headaches, cervical spine roentgenograms will reveal in many cases a loss of the normal lordotic curve or even a reversal of the curve. This may well be a manifestation of the tension, but treating the tension with cervical traction, physiotherapy, a heating pad, and a pressure pad to the neck, while giving some relief, seldom produces more than mild or temporary relief of the headaches. Consequently, this treatment by itself or with the use of sedation is once again obviously insufficient.

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I should like to emphasize at this point that the patients we are dealing with all have one of the glucose tolerance curves shown in the figures. They all have fasting blood sugars within normal limits, although sometimes at the lower limit of normal, and never start out with low fasting levels, as is the case with pancreatic tumors or hyperinsulinism. None of the patients in this group has any evidence of hepatic or pituitary disease or of gastrointestinal malabsorption or disease. Most of them have seen a number of doctors over the past years searching for relief of their symptoms but, generally speaking, without success. There are a few who have come to me stating that they do have "hypoglycemia" as diagnosed by someone else, and, due to the fact that the diet was not rigid enough or that they were not given the supplementary treatment which I have found to be so important, they have not improved sufficiently to satisfy themselves.

The symptoms in this group of 350 cases roughly fall into the following percentages: headaches, 75 per cent, including neckaches; nervousness or tension, 85 per cent; excessive malaise or fatigue, 55 per cent; seizures or black-out spells, 15 per cent; cerebral complaints (speech difficulties, memory loss, disorientation, slowness of cerebration), 25 per cent; dizziness, 15 per cent; visual complaints (blurring, diplopia), 15 per cent; nausea, 15 per cent; lack of coordination, ataxia, paresis, or motor changes, 12 per cent.

In this series of patients, there is a marked predominance of females over males, about 7 to 1. In a number of cases, both mother and daughter have identical findings and usually the mother has brought the daughter in, stating that she feels she probably has the same illness and requesting that I check her. In one family, mother, father, son, and daughter all had identical symptoms and all were completely relieved after treatment.

Generally speaking, in this series, 50 per cent of these patients were "cured" after about three months of treatment, although a number of these will return in several years with identical symptoms after having been free of any difficulty in the interim. Another 25 per cent of the patients are markedly improved and able to go about their normal duties, whereas the last 25 per cent or so are changed very little or not at all by the treatment. Obviously, there is still something that we do not know about this illness and consequently we are unable to treat it completely satisfactorily.

From the laboratory viewpoint, everything is

normal in these patients except the glucose tolerance curve and, in about 50 per cent, the electroencephalogram. The latter is nonspecific according to my interpreters, although they are now reaching the point where they will frequently report "this may represent a metabolic defect of some type." I might interpose here that a few of the patients were hypothyroid and were first treated with adequate doses of thyroid with only minimal improvement in their symptoms and then marked improvement following the usual treatment, which will be described later.

Approximately 100 patients initially had the characteristic glucose tolerance curves. After three or four days of a very high forced carbohydrate diet, the test was repeated and in every case either the curve was unchanged or the abnormalities were intensified. It is very difficult to get private patients to follow up with repeat glucose tolerance curves after they have become asymptomatic, but in the few cases available, the curves have either returned to normal or become much less abnormal. Approximately 20 per cent of the patients have volunteered the information that taking sweets or carbohydrates will initiate or exacerbate symptoms or will produce improvement for a short time, perhaps an hour or two, inevitably followed by a return of their complaints. Approximately 20 to 25 per cent give a history of an intense, insatiable, and irresistible craving for sweets and carbohydrates. It is of interest to note that one patient who was being treated with intravenous nicotinic acid was given this drug in glucose by error and immediately became worse with the precipitation of symptoms, as will be described below. Many patients have been fasted for as long as thirty-six to forty-eight hours, with repeated blood sugar samples taken, and never show any drop to serious levels or any symptoms except mild nervousness, weakness, or drowsiness. We have had a number of patients tell us that, without any treatment except diet, they get along very well until the Christmas holidays, when with the ingestion of considerable amount of CHO all of their symptoms return but immediately disappear a few days after resumption of their high-protein, low-CHO diet.

CASE REPORTS

I should like to describe 3 typical patients very briefly.

Case 1. This patient was a 26-year-old white woman with a flat glucose curve like that in figure 1. She had extremely severe daily headaches for almost two years. She had seen a number of doctors regarding her eyes and sinuses, which proved normal, and had received psy-

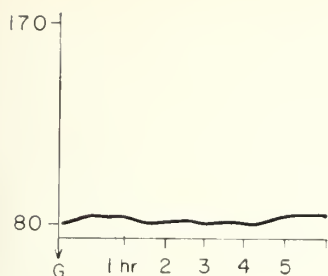


Fig. 1

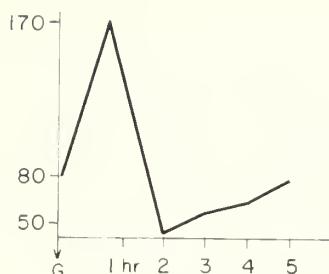


Fig. 2

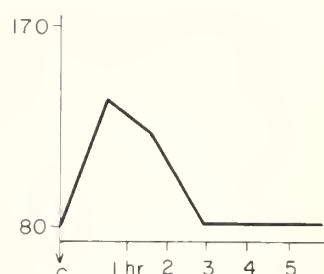


Fig. 3

chiatric therapy and a complete neurologic examination including arteriograms and air studies, all without evidence of pathology and without any relief of her symptoms. She was moderately nervous, and, even when this was relieved by sedation, her daily headaches persisted. They were generalized and dull and frequently lasted all day. She stated that, over the past six months, she had noted a definite sense of fatigue and a lack of her usual excellent mental acuity. Results of a repeat complete neurologic examination were entirely normal except that the electroencephalogram revealed minor diffuse nonspecific changes. Results of her physical examination were normal. The five-hour glucose tolerance test revealed a fasting blood sugar of 70 mg. per cent and then hourly specimens of 92, 98, 70, 74, and 72 mg. per cent. She was placed on the usual treatment and within a week was free of headaches and all of her abnormal complaints. She has been followed now for two years with no recurrence of her symptoms except "when I forget and eat some sugar and excessive carbohydrates my headaches always return." At my suggestion, she has tried taking even moderate excesses of carbohydrates periodically but always with recurrence of her complaints.

Case 2. This patient, with the type of glucose tolerance curve seen in figure 2, was a 38-year-old white mathematician. He stated that a diagnosis of narcolepsy had been made on him previously, based on the fact that, over the preceding three years, he had become increasingly irritable and sleepy and had a sense of "complete and chronic exhaustion." He fell asleep several times while driving his car and had numerous episodes of sleepiness. He had had a complete neurologic examination elsewhere, with the diagnosis of narcolepsy, and Dexedrine, Dexamyl, and various other drugs had been prescribed. None of these had any effect on his symptoms and only produced further nervousness and insomnia. Although he was a trained mathematician he noted that, over the past few months before the present examination, he was unable to add his checkbook entries without making many errors; his wife stated he had had a complete personality change over this period, with great irritability, a short temper, and marked nervousness, all of which were entirely contrary to his usual personality. On a number of occasions in those few months, he had apparently gone to sleep and fallen out of his chair and on several other occasions he had had momentary blackouts and had fallen down on the street. He travels much and noted that, if he kept candy bars with him while driving and ate one approximately every thirty minutes, he would just barely be able to stay awake. However, if he discontinued this, he would feel much worse; taking a single candy bar would produce mild relief of his symptoms with an exacerbation of them approximately

one or two hours later. A complete neurologic examination yielded normal results, but his electroencephalogram revealed nonspecific, abnormally slow waves in both parietal zones. His glucose tolerance revealed a fasting level of 94 and then hourly levels of 170, 55, 60, 76, and 90 mg. per cent. After the usual treatment was begun, he made a slow but definite recovery and, at the end of thirty days, stated that he felt 90 per cent improved. After three months, his electroencephalogram returned to normal and he was completely free of any symptoms. He has been treated with nothing but diet for the past year and has remained completely symptom-free.

Case 3. This patient was a 49-year-old white woman with the type of curve seen in figure 3. She had a six-year history of severe generalized or left frontal headaches, with numerous neurologic examinations and psychiatric treatment by several physicians, all without success. For three months before seeing me, she experienced definite staggering gait and ataxia, garbled speech at times, and a noticeable memory loss for both recent and past events, as well as for even simple matters. Her husband also stated that she had a great deal of mental confusion and that, whereas she had previously been a very alert and intelligent person, she now appeared to be stupid and slow. She was quite disgusted with the medical profession after these years of studies and treatment, all without effect. She had been taking excessive doses of aspirin, Empirin, and codeine in an attempt to alleviate her severe headaches. She gave a long history of excessive ingestion of carbohydrates, but otherwise there was nothing of note in her systemic review. At the time she was seen, she was extremely confused, even as to the time of day or date, and had a staggering gait, but results of neurologic examination were otherwise entirely normal. Her electroencephalogram was abnormal with diffuse nonspecific changes. Her glucose tolerance over the five hours was a fasting level of 86 and then hourly levels of 130, 112, 78, 82, and 80 mg. per cent. This woman has now been followed for nine months and is completely asymptomatic, and her electroencephalogram has returned to almost normal. She is lavish with her praise for the complete relief of all her symptoms for the first time in some six years. According to her husband, she has returned entirely to normal from the mental point of view.

Case 4. Another patient with the type of glucose tolerance curve seen in figure 1 was a 44-year-old executive who gave a three-year history of frequent blackout episodes and occasional seizures, all of which were followed by several hours of extreme mental confusion, garbled speech, and weakness to complete paralysis of the right arm and leg for varying periods. Previous diagnoses were

epilepsy, brain tumor, and psychosis. Results of neurologic examination were entirely normal, although after episodes precipitated by the ingestion of glucose he would frequently have markedly decreased reflexes on the right side or positive Babinski signs of a transient nature. He stated that 90 per cent of his attacks were precipitated by the ingestion of carbohydrate, and we were able to reproduce these attacks on a number of occasions with glucose given orally or intravenously. This patient has now been followed for eighteen months and is completely free of symptoms and has no further mental confusion.

TREATMENT

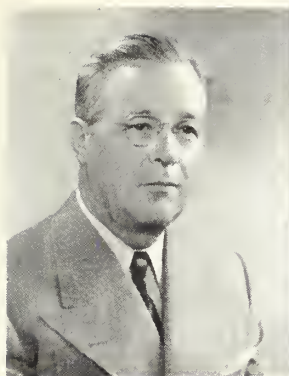
As mentioned previously, I have gone to the extreme in attempting to first treat these patients with one isolated type of therapy, such as only sedatives or tranquilizers, physiotherapy and cervical traction to the neck, psychiatric care, nicotinic acid, or plain high-protein, low-carbohydrate diet; in all cases there has been little or no change in their symptomatology. Consequently, I have come to use a set routine in these patients after having experimented as above. It has also been noted that coffee has a deleterious effect on a number of patients, and many have failed to improve until it was withdrawn. Consequently, treatment consists of a strict high-protein, low-carbohydrate diet; heavy doses of vitamins both by mouth and by injection; no coffee, although Sanka is permissible; mild sedation; 100 mg. of nicotinic acid four times a day, before meals, and at bedtime; and supplementary protein feedings three times a day, between meals and at bedtime. The more seriously ill patients with extreme symptoms receive intravenous nicotinic acid, 100 to 200 mg. in 250 cc. of normal saline, between meals and at bedtime. It is of interest to note here that a number of patients are markedly improved for several hours after receiving intravenous nicotinic acid, and several of them have even requested permission to continue the injections while outpatients. I am not able to explain the rationale of this treatment but have learned from long and arduous experience that the combination mentioned above works much better than anything else I have tried.

A very excellent response has been achieved in at least 75 to 80 per cent of this fairly large number of patients. Many of them are almost remarkable in their improvement. The improvement has persisted and been maintained even after their various medications have been dis-

continued, usually about three months after treatment was started. I instruct these patients to remain on a fairly rigid high-protein, low-carbohydrate diet indefinitely, although occasionally some of them are able to abandon it without any deleterious effects. However, the vast majority will be unable to tolerate any very large amount of carbohydrate for an indefinite period. Among the patients are 3 doctors' wives with long histories of headaches treated in every conceivable fashion without relief, all of whom are now completely asymptomatic as long as they remain on a high-protein, low-carbohydrate diet and all of whom have prompt return of headaches, nervousness, and irritability after excessive or even moderately heavy carbohydrate intake.

We have described only some severe cases, but many patients with milder symptoms are also called neurotic or referred to the psychiatrist. Consequently, we feel that the ability to recognize and treat them is extremely important, and, certainly, the results as expressed by the patients themselves are most gratifying. Unfortunately, most of these results are judged purely on a clinical basis, although those in patients with neurologic manifestations are more dogmatic. Nevertheless, I feel that this syndrome is extremely important because of its frequency and serious diagnostic errors, and I hope that this paper will stimulate other physicians to search out patients suffering from this disorder, so that they may be relieved of their distress and so that, as time goes on, we may learn more about it. The condition appears to be the result of some type of defect in carbohydrate metabolism and is obviously closely related to the neurologic system. In an attempt to have some type of a control, I recorded glucose tolerance curves over a five-hour period in 10 medical students, who by history were presumably on a normal diet. In all 10 cases, a perfectly normal glucose tolerance was found initially and there was no change in the glucose tolerance curve after a week of high-carbohydrate intake which much exceeded what was normal for them. These findings would tend to indicate that normal persons are able to handle the stress of a high-carbohydrate diet, in contrast to the patients described above, although the reasons for these patients' inability to either tolerate or utilize carbohydrates in the diet are not apparent at this time.

This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.



BYRL R. KIRKLIN, M.D.
1888-1957



HARRY M. WEBER, M.D.
1899-1958

The Kirklin-Weber Lecture

Roentgen Diagnosis of the Upper Gastrointestinal Tract

Historical Development

LEO G. RIGLER, M.D.

Los Angeles

I AM DEEPLY STIRRED by the privilege of presenting this first lecture in honor of Drs. Byrl R. Kirklin and Harry Weber, for I counted these two physicians as my dear friends for many years. Our close professional association through the graduate school at the University of Minnesota and joint enterprises in our scientific community were only a part of the picture. The other part was the lasting friendship founded upon these cooperative endeavors.

One of my fondest recollections of Dr. Kirklin concerns the institution of the Carman Lecture, now a fixture at the meetings of the Minnesota State Medical Association. Many years ago, I was struck with the fact that as yet no formal effort had been made to honor the name of Dr. Russell Carman. At the same time, the Minnesota Radiological Society was an infant group striving for a place of importance among the state medical organizations. It occurred to me that the Society would honor itself by perpetuating the name of a man who had brought such great distinction to the state, that is, by the es-

tablishment of a lecture in honor of Dr. Carman. I immediately telephoned Dr. Kirklin and, as I expected, received prompt and very enthusiastic approval. I should point out that Dr. Kirklin was my senior and the matter really concerned the Mayo Clinic group, but in his mind there was no thought of protocol. He accepted the idea and soon assured me of forthcoming financial backing. This is one of the innumerable examples I could cite of his consistently cooperative spirit.

You will note that the title of this address is "The History of the Development of Roentgen Diagnosis of the Upper Gastrointestinal Tract," a significant adventure in the spectacular expansion of medical diagnosis during the past half century. Recently, at a conference of the American Association of Medical Colleges, I followed a noted surgeon on the platform. He had spoken eloquently of the history of surgery, especially its evolution since the early part of the fourteenth century. By contrast, my own short sketch of the history of roentgenology began just before the twentieth century. I could, however, point with pride to a rapidity of development and expansion of ideas, which compensate, in some measure at least, for the extreme youth of my specialty.

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The personalities and lives of Byrl Kirklin and Harry Weber are intimately bound up with the progress of medicine, especially with roentgen diagnosis. Indeed, they reflect the manner of its development in this country and especially the evolution of gastrointestinal diagnosis.

One of the striking characteristics of Dr. W. J. Mayo was his extraordinary ability to pick out young men who had the potential that would preserve and enhance the stature and work of the clinic. One of these flashes of prescience brought to his attention the young Kirklin, working in a small community in Indiana, largely self-trained in radiology, as were most of the men at that time, but exhibiting an extraordinary degree of ability and aptitude. He was brought to the clinic for a short period, under difficult circumstances—a very young man exposing his scientific wares to the scrutiny of such veterans in the field as Russell Carman, A. B. Moore, and Charles Sutherland. The roentgen eyes of Dr. Russell Carman were critical indeed, but within Dr. Kirklin they saw a great potential. As soon as possible, therefore, the young radiologist was appointed to the staff of the clinic. What he demonstrated was a new technic for the examination of the gallbladder. This was before the days of cholecystography, and the gallbladder was one of the blind spots in roentgen diagnosis. True, gallstones had been demonstrated in 1901 by Emil Beck and others, but beyond finding calcified stones, little else was accomplished by roentgenographic examination. The work of George and Leonard opened a new field of endeavor which Kirklin assiduously pursued. Looking back, we are inclined to believe, as did Carman, that their idea that the abnormal gallbladder would be visible in the roentgenogram was fallacious, but Kirklin's interest in technic led to a greatly improved delineation of gallstones and eventually to many brilliant improvements in the technic of cholecystography. A new series of original contributions, including especially the use of the lateral decubitus position, the description of benign tumors of the gallbladder, and many other diagnostic signs soon made him known internationally as the Mr. Gallbladder of the roentgen world.

Dr. Kirklin, also possessed of "x-ray eyes," has in turn reared a generation of disciples, among them heads of departments, research workers, scientists, and, more especially, superbly practicing radiologists. He exhibited this rare insight when he selected Harry Weber, first as a resident and then as a permanent member of his staff. Between them they followed the great tradition, first established by Russell Carman,

that the Mayo Clinic and Mayo Foundation were in many respects the fountainhead of knowledge for the practice of roentgen diagnosis, most especially, of course, in the gastrointestinal tract. Kirklin was gifted with an extraordinary talent for conveying to a group the results of painstaking and meticulous endeavor. Because of this, scarcely anyone was invited to more national and international meetings or asked to speak on more occasions on the various subjects in which he excelled.

In the case of Dr. Kirklin, I suspect the landmark in his activity, the acme of his ambition, was the establishment of the American Board of Radiology. Here, his extraordinary capacity as a mold of men, his ability to keep a heterogeneous, individualistic, egocentric group of physicians working together smoothly and successfully, made it possible to establish an organization which has significantly helped to elevate the practice of radiology in the United States to its present high status. For many years he also was secretary of the Advisory Board for Medical Specialties, exhibiting wisdom, moderation, and superb organizational ability. I will not attempt to recite Dr. Kirklin's complete biography. Suffice it to say he has held practically every office of importance that medical societies could extend in these United States, as well as many honorary memberships in societies abroad. His record with the United States Army was one of great distinction; without doubt, he established radiology in the army on a firm and lasting basis. His work during World War II in inspecting and giving advice to the various radiologic installations of the army and of the air corps was one of his really notable achievements.

Dr. Kirklin's outstanding characteristics, I believe, were his serenity, his well-ordered, well-disciplined mind, and his ability to weigh all factors completely and fairly and to persuade his colleagues to follow his middle-of-the-road guidance which usually led to the best achievements.

Harry Weber, a native Minnesotan and a graduate of the University of Minnesota, began his professional career at the Mayo Clinic as a graduate student in radiology and continued as a staff member until his untimely death. He impressed everyone with his warmth, his deep sincerity, and his complete honesty. He and I had many intimate talks about the situation of radiology in general, but specifically at the Clinic and at the University in Minneapolis. Never did I feel the slightest dissembling, the slightest hint of anything but the strictest honesty, the complete desire to do the right thing for others. Honored as a relatively young man by such distinctions as

being chief of instruction courses for the American Roentgen Ray Society, president of the same society, chairman of the Radiology Section of the American Medical Association, the winner of many awards and honorary memberships, Dr. Weber contributed greatly to radiology, particularly in this area of the gastrointestinal tract. He was responsible for the development of the double-contrast method for examination of the colon in this country, and, in general, for making the roentgen study of the colon as significant a procedure as it is today. His work on the small bowel, on the stomach, and in many other fields of roentgen diagnosis has contributed substantially to the advancement of the specialty. In a superb way he carried on the tradition of the great heads of the radiology department at the Mayo Clinic. He inspired uncommon confidence, affection, and loyalty in his residents and friends. I knew personally that if I ever needed any help in any direction, regardless of what the cost might be to Harry himself, he would respond. All of us will mourn him. We have lost a great radiologist and a very dear friend. Both Doctors Kirklin and Weber exhibited scientific and personal characteristics which have inspired physicians in all fields of medicine and will be a source of inspiration for generations to come.

As I try to recite briefly the history of the development of roentgen diagnosis of the upper gastrointestinal tract, a history in which the radiologists of the Mayo Clinic have taken such an important part, I am reminded of a statement by Henry Hazlitt. Referring to the numerous volumes which have been written about William Shakespeare, he says: "If we wish to know the force of human genius, we should read Shakespeare. If we wish to know the insignificance of human learning, we may read his commentators." As I reviewed the work done in our field from its very beginnings, I felt keenly the insignificance of the historical review as compared to the making of the history itself.

The discovery of a new type of radiation by Wilhelm Conrad Roentgen in 1895 had a profound impact on science in general and on the practice of medicine in particular. Not the least of its revolutionary effects was developed in the field of diagnosis. A new chapter in the history of medicine was written with that epoch-making discovery. The writing on the first pages may have been hesitant and irregular but here and there, even during the first few years, can be observed broad, bold strokes that were prophetic of the advances that were to come.

In 1896, investigators and medical authorities, who considered the usefulness of Roentgen's rays

in medical practice, expressed opinions ranging from extreme skepticism to surprising optimism. Indeed, it is a remarkable, an astonishing phenomenon that the possibilities of x-ray diagnosis were so quickly and enthusiastically perceived. It would be hard to find anywhere in the annals of medical science such a rapid acceptance of a new discovery. In the minds of medical men, a new horizon had been discovered. The possibility of submitting to visual inspection, in the living subject, structures which heretofore could be seen only in the surgery or on the autopsy table, was so attractive, so exciting, that the impulse toward investigation and experimentation was well-nigh irresistible. Confined to the lesser senses of perception, touch and sound, with the visual senses restricted to limited use in an indirect way, medical diagnosticians always labored under great disability. The results of their studies were not inconsistent with such handicaps, as any comparison of medical diagnosis with autopsy findings, even during the second decade of the century, will aptly attest. The opportunity of performing a veritable "autopsia in vivo" must have been dazzling to the physician who appreciated fully the limitations of his methods and the possibilities of the new procedure. The importance of visual testimony has been emphasized in the aphorisms of many lands; the physician, like other human beings, places greater reliance upon ocular perception than on the impression gained from any other sensory organ. It is no wonder, therefore, that efforts toward improving and utilizing this medium began so early and were pursued with such determination in our period. Many were literally searching for light in dark places.

In the history of medicine there is nowhere a more fascinating chapter than that which relates the story of the introduction and amplification of various contrast media for roentgen diagnosis. It was at once apparent to Roentgen himself, and shortly thereafter to the medical colleagues to whom he first communicated the results of his research, that the nature of any tissue would determine the degree of its opacity to the x-rays. Because, in the early experiments, only the bones and metallic objects were clearly visible, it was first assumed that the utility of the method would be limited to the skeleton or to the search for metallic foreign bodies. Nevertheless, these first halting steps were rapidly followed by efforts to make visible the esophagus and the gastrointestinal tract. By March of 1896, metallic sounds were being put into the esophagus of cadavers. Strauss shortly afterward tried iron oxide and bismuth subnitrate in the form of

capsules within the esophagus. Likewise, early in 1896, Hemmeter, in this country, introduced capsules of reduced iron and rubber bags containing lead solution into the stomach of living individuals but without any real success in demonstrating these structures.

Following Hemmeter's work, Wolf Becker, also in 1896, tried to fill the stomach and bowel with a lead solution without practical results. No doubt the suggestion of Bowditch, Professor of Physiology at Harvard, to Walter Cannon, in the fall of 1896, that he try to study the process of deglutition by means of x-rays, was the beginning of the first successful use of contrast media in the gastrointestinal tract.

On December 29, 1896, Cannon, using capsules of bismuth subnitrate, demonstrated before the American Physiological Society the act of swallowing in a goose. He followed this by putting contrast material, a mixture of bismuth subnitrate and milk, into the stomach of the cat to study gastric physiology. He reported these experiments on May 4, 1897, also, to the American Physiological Society.

Perhaps the first published account of results in the living human being was made by Rumpel on April 20, 1897, when he disclosed that pouring 300 cc. of a 5 per cent suspension of bismuth subnitrate into a dilated esophagus had enabled him to observe it fluoroscopically. Roux and Balthazard gave the first report, in 1898, on the study of the motor function of the human stomach, using bismuth subnitrate in water and syrup. The experiment was actually performed in 1897. These French experimenters, even at this early time, conceived of the idea, first proposed by McIntyre in 1896, of cinematographic x-rays. They actually carried out some motion studies in the frog, using a plate-changing apparatus. As we know, neither McIntyre's experiments nor theirs were sufficiently successful to permit us to make x-ray motion pictures until a great many years later.

The initial work on human beings in this country was undertaken by Francis Williams of Boston and recorded in his book first published in 1901. Assisted by Walter Cannon, on September 23, 1897, he gave an ounce of bismuth subnitrate with milk and bread to a 10-year-old child; he later repeated this on several other children, thereby studying the outline, evacuation, and peristalsis of the stomach with the fluoroscope. Williams also records his unsuccessful effort to make an x-ray examination of a patient with a palpable carcinoma of the stomach.

In 1898, Boas and Levy-Dorn in Berlin, used capsules filled with bismuth to occlude the

esophagus and localize the site of obstruction. Holzknecht, in Vienna, began using bismuth subnitrate free in the esophagus at this time as well. It is interesting that both Williams in Boston and Holzknecht in Vienna, at the same time, suggested the use of gas, such as air or carbon dioxide, to make the stomach visible by inflation.

All such efforts were fragmentary and not highly successful until Rieder, in 1903, formulated the bismuth meal. With various modifications, this remained for many years the standard contrast medium for oral administration in the roentgen study of the stomach.

Since the bismuth salts were difficult to purify and occasionally proved to be toxic, substitutes were sought. Barium sulfate proved to be a far better and much cheaper substance with no toxicity. First proposed by Bachem and Gunther in 1910, it has been used ever since. The original Rieder meal consisted of bismuth in a thick gruel, much too thick to permit delineation of the mucous membrane pattern. Later, the medium used was buttermilk and, in fact, this mixture was still being used when I began to do fluoroscopy in the early twenties. Other contrast substances have been used, such as colloidal suspensions of barium and of thorium compounds, in an effort to avoid impaction and obstruction. More recently, watery mixtures of organic iodide compounds have proved useful, especially when aspiration is feared or when there is any possibility of perforation or obstruction. Gases have been introduced by way of a tube, by means of carbonated drinks, and by use of Seidlitz powders combined with barium and given in small amounts so that a double contrast is obtained. Gas has also been used to distend the stomach sufficiently to flatten out the gastric rugae and thus help differentiate these from mucosal tumors.

With almost its first breath of life, the roentgen method of examination of the gastrointestinal tract divided itself into 2 major procedures. Roentgen had discovered almost simultaneously both the fluorescent effects of x-rays on a screen coated with crystals and the photographic effect on a sensitive emulsion. Not long afterward, both Michael Pupin and Thomas Edison developed fluoroscopic screens which were far more practical.

The equipment at this early time was primitive and exposure time for roentgenograms of thick portions of the body was twenty to thirty minutes; hence, it was impossible to demonstrate effectively a moving organ on a roentgenogram. It was not until 1903 with the improvement of the power source and the development of in-

tensifying screens that the exposure time was reduced to fifteen or twenty seconds. With the invention of the rectifying transformer by Clyde Snook and further improvement of the intensifying screens, exposure times were reduced to the range of a second or less.

Already, in the second year of the utilization of x-rays for diagnosis, there was conflict as to the respective merits of fluoroscopy and radiography. The great advantages of fluoroscopy in a wide variety of conditions, including, especially, the gastrointestinal tract, were extolled before a meeting of the London Roentgen Society in 1899, but there was already some criticism of this practice because of the possibility of its injurious effects. In 1903, and thereafter, a group of Viennese radiologists, headed by Guido Holzknecht and including such other distinguished scientists as Strauss, Rieder, Schwarz, Groedel, Albers-Schonberg, and Haenisch, presented numerous papers dealing with fluoroscopy of the stomach and describing what they called "symptom-complices," the secondary signs of gastrointestinal disease. The very interesting monograph by Holzknecht and his associates, published in 1905, presents in some detail their fluoroscopic observations of the stomach.

The Viennese group had, by this time, developed to some degree the so-called "distinator," a wooden spoon for manipulation of the stomach to avoid the use of the hands, but they were not yet fully aware of the extreme dangers to which they were subjecting themselves during the course of fluoroscopic examinations. Holzknecht, for example, suffered from severe burns on his hands in his later years. A good deal of the discussion centered around the physiology, form, structure, and activity of the stomach at that time. In addition, they laid emphasis upon spasm, obstruction, abnormalities of peristalsis, and other secondary signs to indicate the presence of lesions, especially tumors. Holzknecht does illustrate in drawings, however, some definite pictures of gastric tumors of large size, indicating that there was some attention to morphology as well as function.

In this country, George Pfahler of Philadelphia had already published a paper in 1905 on roentgen-ray observations of the physiology of the stomach. No doubt, he was one of the first in this country to use x-rays effectively in the gastrointestinal tract. Also in 1905, Henry Hulst demonstrated roentgenograms of the stomach at a meeting of the American Roentgen Ray Society and devoted his presidential address in 1906 to this subject. He was followed shortly by Edward Skinner of Kansas City, by Henry

Pancoast of Philadelphia, and by James Case, to whom I am greatly indebted for some of the memorabilia of this period.

Case described to me in some detail the primitive character of the equipment that he used for fluoroscopy. He had an ordinary horizontal massage table with good rollers on it so it could be moved easily. Underneath was the x-ray tube in a fixed position. Blankets were thrown around the tube to keep out the light, and the table with the patient on it was moved around the tube. Case used a hand fluoroscope (completely unprotected) to begin with, then a larger screen which was better protected and was movable. Not until 1910 did he obtain from Germany an apparatus which could be put in the upright as well as the horizontal position, probably originally designed by Haenisch of Hamburg.

In 1910, a notable development in the diagnosis of disease of the stomach occurred when Martin Haudek, a member of the Viennese radiologic group, described the niche sign of gastric ulcer. Felix Fleischner, now in Boston, who was Haudek's assistant at one time, has given me some intimate glimpses of the background. Holzknecht and his students had repeatedly made the diagnosis of hourglass stomach, an observation which is recorded in his book as early as 1905. When one of these patients was operated upon, the surgeon, in typical fashion, said to Haudek: "You have been wrong on 2 counts. You saw an hourglass stomach and there was none; you missed the ulcer itself which certainly was there." Haudek reviewed the glass plates which had been preserved and, using what we now please to call the "retrospectoscope," he saw a projecting, pocketlike irregularity just opposite the indentation which they had called an hourglass deformity. At about this time Reich published 2 cases of such ulcer pouches, which he called diverticulum structures. With the large material at the Viennese General Hospital, Haudek soon was able to report on 11 proved cases and in a very few months he had 25 cases in which he could definitely demonstrate the gastric ulcer as a protrusion through the wall of the stomach.

When Haudek went to a meeting in Berlin to demonstrate this new sign, the gastric niche, the discussor remarked, "Oh, these ulcers just occur in Vienna where they have spicy foods and a good deal of imagination. We don't have them in Berlin." Not long afterward, however, the Berliners and radiologists all over the world were finding the niche and making the direct diagnosis of gastric ulcer. By 1911, Haudek was already attempting to distinguish between be-

nign and carcinomatous ulcer by means of roentgen study. The monograph by him and the surgeon, Paul Clairmont, on "The Significance of the Radiology of the Stomach for Surgeons," published in 1911, is most illuminating. The importance of the findings went beyond their immediate significance. They focused attention on the possibilities of demonstrating morphologic changes, the actual pathologic anatomy of the stomach.

The differences of opinion as to the respective merits of fluoroscopy and radiography in the examination of the stomach became apparent very early in the history of roentgen diagnosis and persisted for a long period of time. According to Fleischner, Holzknacht would speak of "living fluoroscopy," comparing it to "dead radiography." By 1912 Russell Carman and Louis Gregory Cole in this country and Gosta Forssell in Sweden began to influence gastrointestinal roentgen diagnosis. They participated actively in the controversy concerning the 2 methods. Carman had begun his career in St. Louis and had already written some papers about medical roentgenology as a specialty and about urinary calculi as far back as 1907. His first contributions in the gastrointestinal field began about 1911. In 1912 we find in the *Journal of the American Medical Association* an article by him on cardiospasm and again, in 1913, one on the technic of roentgen examination of the gastrointestinal tract and its interpretation. It is significant that he was already discussing the differential diagnosis of gastric cancer and benign ulcer in 1913, and by 1914 he had detailed the secondary signs of duodenal ulcer.

Carman's notable book, "The Roentgen Diagnosis of Diseases of the Alimentary Canal," first published in 1917, had an enormous influence upon roentgen diagnosis. He became the foremost advocate in this country of the fluoroscopic method, agreeing generally with the ideas emanating from the Viennese group. Though they used the fluoroscope primarily for demonstrating the so-called symptom-complex, the secondary signs of stomach lesions, they also attempted to delineate actual morphologic changes. Cole, on the other hand, abandoned the fluoroscope at an early date, and by 1909 began making 10 to 12 plates—and they really were plates at that time—of the stomach, in a number of postures. He developed what he called serial roentgenology, using a special table. It was, in effect, an effort to simulate what was observed on the fluoroscopic screen but could be seen in better detail in the roentgenogram which then could be examined at leisure. At a meeting of the Missis-

sippi Valley Medical Association in 1912, the striking conflict in points of view was exhibited. Skinner of Kansas City advocated the fluoroscopic method which Carman and Mills were already practicing in St. Louis. Shelby, who was then the roentgenologist at the Mayo Clinic, also advocated fluoroscopy and implied, at least, that films were relatively valueless in the examination of the gastrointestinal tract. Cole, of course, advocated the serial film method. We have passed through a period of controversy in this matter which I believe has been resolved in the minds of most radiologists by the sustained conclusion that each agency is supplemental to the other.

The work of Louis Gregory Cole and his associates emphasized the importance of the delineation of the detailed anatomy of the stomach; his teachings were most influential. He was among the first to attempt to study the gastric mucosa and to make the diagnosis of postpyloric ulcer.

The founder of the Swedish School of Radiology, Gosta Forssell, made his major diagnostic contributions in the examination of the stomach. In 1908, he described the Forssell fluoroscope, designed primarily for positioning the patient in order to obtain what he called "focused" roentgenograms. In a later series of papers he delineated the roentgen anatomy of the stomach and its physiology; his terminology is still used today. His description of the independent motion of the mucous membrane of the stomach aroused a new interest in superficial lesions. Forssell advocated distributing a thin layer of the opaque mixture in order to demonstrate the mucosal pattern. Earlier attempts along similar lines had been made by Holzknacht and Brauner in 1906 and Von Elicher in 1911.

Eisler and Lenk in Vienna in 1921 used small amounts of barium in water, with pressure, to delineate the mucosal surface. Two years later, Bastrup obtained fairly good films of mucous-membrane folds by inflation of the stomach with barium powder and air. None of these procedures proved to be practical. In 1923, however, Richard Rendich of Brooklyn, later chief of the Department of Radiology at the Long Island Medical College, described the first successful efforts to examine the mucosa for pathology, using a special meal of barium mixed with acacia and putting the patient in various positions by means of a tilt table. Rendich demonstrated various abnormalities of the mucosa itself more effectively than his predecessors.

Beginning in 1917, Ake Akerlund, Forssell's brilliant student, using various pressure devices, studied the duodenum with a view to demonstrating postpyloric ulcer, hitherto seen only by

the surgeons and the pathologists. Akerlund's description of the characteristic deformity of the duodenum which indicates the presence of an ulcer and his later demonstration of the niche in the duodenal bulb were milestones. He also described hiatus hernia in some detail and directed attention to the frequency of gastric diverticula. At about this time the "spot" filming which is so characteristic of present-day gastric roentgenology was brought to a greater state of perfection by Hans Heinrich Berg of Hamburg. He developed a number of methods, including rubber bags, cones, and belts of one kind or another for pressure purposes and altogether contributed greatly to the advancement of gastrointestinal diagnosis.

By this time, Carman had published the second edition of his work in which he emphasized, to a greater degree, the positive morphologic signs of diseases of the stomach. We have come to regard such evidence as the only true indication of a disease process.

A consistent thread can be detected in the evolution of the roentgen diagnostic criteria of disease. The first steps are often hesitant and groping as the morphology of a disease process is first recognized in the roentgenogram. The organ is then restudied to determine its normal appearance, since anatomic variations and other deviations lead to false-positive diagnoses. When such aberrations are clarified and the normal appearance of the organ is fully recognized, specific diagnostic criteria are laid down for the recognition of the roentgen signs of the disease. About this time, the brashness and overconfidence of youth assail the investigators, so that the roentgen findings come to be considered as pathognomonic of the disease. As time goes on and experience produces its usual salutary effect, the simulations of the roentgen appearance by other disease processes of different nature and etiology are revealed, so that the specificity of the signs no longer appear valid. Finally, a more conservative point of view prevails and a reasonable interpretation of the significance of the roentgen findings is obtained.

This same process certainly affected the development of roentgen diagnosis of diseases of the stomach. Carman's great contribution was the clarification of these signs, and his work was followed and amplified, and in many cases corrected, by Kirklin and Weber and their associates. Special signs, for example, were brought out; the most notable is the meniscus sign first reported by Carman in 1921. The misinterpretations of Carman's report made it necessary for Kirklin to redescribe Carman's original obser-

vations and to clarify the nature and significance of this sign and the differential diagnosis of malignant ulcer.

All the studies from this time on necessarily involved much greater detail in the examination of lesions of the stomach. No great discovery nor great changes in technic occurred. Nevertheless, the numerous studies, such as reported by Kirklin on the differentiation of benign from malignant lesions, the art of fluoroscopy of the stomach, the dangers of fluoroscopy, the technics of demonstrating lesions of the cardia of the stomach, and so forth, were of great importance in the development of our present-day exactitude in diagnosis. Many other contributors might be mentioned in this regard, but none of them made contributions of such an order as to produce a great impact upon the evolution of roentgenology of the gastrointestinal tract.

One development which should be considered more specifically is that related to photofluorography and cinematography. The work of McIntyre and of Roux and Balthazard in 1896 and 1897 has already been mentioned. In a sense, practical photofluorography dates back to the pioneer experiments of McIntyre and, likewise, of Bleier in 1896, but they were brought to real fulfillment by D'abreu in Brazil in 1936. Introduced in this country by Potter, the procedure for making a photographic record of the fluoroscopic image on small-sized film was rapidly adopted for examinations of the chest. At the same time, various methods of direct cinematography came into effect, particularly through the work of Ruggles, Hans, Jarre, and many others. It should be noted that as early as 1930, Purcell designed a table which permitted rapid direct radiography of the stomach. These were efforts to move films rapidly enough to make multiple roentgenograms which could be transposed into motion pictures. This procedure has been largely abandoned because of the development of indirect roentgen cinematography—that is, the photograph of the fluoroscopic image. The major work in the gastrointestinal tract was accomplished both by Janker in Germany and by Ramsey and his associates at the University of Rochester in New York. The process of photofluorography, without cinematography, was soon applied to the stomach and later to the colon. For many reasons, this has not been as successful as in the case of the chest; nevertheless, because of its low cost and the rapidity of execution, the method has been used to do routine examinations of the stomach in symptomless individuals. The factor of radiation hazard is much greater under these circumstances than it is by

ordinary radiography, and the difficulties of doing such an elaborate examination upon apparently normal individuals have inhibited the development of the program.

The delineation of the stomach and duodenum by means of roentgen examination have become such an accepted part of medical practice that today it is difficult to look back upon the time when they were not in effect. With the improvement of fluoroscopic screens and, especially, now with the development of an image amplifier, the possibilities of improved fluoroscopy, of photofluorography, and especially of cinematography, are being thoroughly explored. Already we have had extensive studies of the swallowing mechanism and the activity of various portions of the esophagus. Numerous studies of the stomach in animals and now in human beings have also been done. The degree of radiation exposure is still a limiting factor but, with the use of image amplifiers and the transference of the product of the image amplifier to small film, the method has become much more practical and will give enormously increased opportunity for detailed diagnosis. No doubt, in the future more detailed views of the stomach may be expected so that the diagnosis of minor mucosal changes, such as in gastritis, and the determination of the nature of certain functional abnormalities may be determined with far greater accuracy.

In recent years many investigators have been absorbed by attempts to undertake survey examinations of the stomach and, in fact, of the entire gastrointestinal tract in apparently normal individuals. Particularly, it has been our concern to discover a means of detecting cancer of the stomach and of the colon in their presymptomatic stages. At the University of Minnesota for a number of years, we conducted an extensive experiment in this direction, first by examining patients with pernicious anemia routinely at semiannual intervals and later by examining a larger group of older individuals selected largely on the basis of the presence of achlorhydria or hypochlorhydria. The x-ray method used was the conventional one, namely, fluoroscopy, with films made under fluoroscopic control with compression and routine conventional films in various positions. Further efforts in this direction have been made, using fluoroscopy alone or photofluorography alone, exemplified especially by the work of Roach and Morgan and Wigh and Swenson, as well as a number of others. This program was also pursued extensively by Robert Sherman at the Memorial Hospital in New York. It is evident from the results of our examinations as compared with those of investigators using the

simpler, less expensive and less time-consuming methods, that conventional elaborate examination is the only one which will detect large numbers of small presymptomatic tumors. My own experience has indicated that it is possible, with some degree of regularity, to find lesions in the stomach before the onset of symptoms when the lesion is a centimeter or more in size. Obviously, more errors are made under these circumstances than in examinations for symptomatic lesions, but, on the other hand, it is clearly evident from the results that a greater salvage will occur if such lesions can be detected. However, the expense, in terms of personnel required by such an examination, is of such an order as to make it impractical for general use. We can only hope that more efficient and less time-consuming methods can be achieved which will permit wider use of a procedure to detect cancer of the stomach in its presymptomatic stage and when it is small in size.

Can anything of practical importance be accomplished by the routine roentgen examination of the stomach? If one were to believe the pessimists, those who adhere so strongly to biologic predeterminism—I would like to call it predestination—such studies would be of little value, since the size and stage of the tumor would not affect its curability to any degree. Granted that carcinoma of the stomach is a highly malignant tumor, there is, nevertheless, good evidence that size is an important factor in curability and presymptomatic diagnosis results in far greater salvage after surgery than in the ordinary symptomatic case. Certainly, the challenge of discovering minimal lesions in their presymptomatic stages is one which still confronts the medical profession and especially the young radiologist. The need for discovering pathology in its minimal form should appeal to the ingenuity and inventiveness of the present generation. Much remains to be achieved in roentgen diagnosis.

As we view the accomplishments of our predecessors, the giants of the early part of the century, we feel at once humble and proud of what has been done, at once respectful and determined to do more ourselves. Perhaps, then, this historical review is not quite as insignificant as it appeared to me at first. For history, after all, is a chart, a map to guide us on future voyages of discovery. And its lessons may well serve as beacons lighting our way to that end toward which all of us in the healing arts must steer—greater health and happiness for mankind.

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Adenocarcinoma of the Fundus of the Uterus

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THE METHODS of treatment of adenocarcinoma of the uterus have varied little in twenty-five years. Despite this, the over-all survival rate has definitely improved. The progress may be due to early recognition or diagnosis of the disease, to the influence of improved operative techniques, or to our eager response in treatment of the more favorable cases.¹ However, if beneficial results are to continue in increasing numbers, we must apply even more of our energy and direct even more of our attention to early diagnosis and to prompt institution of therapy. This, in my judgment, is the success to any method of treatment.

DIAGNOSIS

Women must be educated to the importance of frequent gynecologic examinations and to the significance of irregular vaginal bleeding and spotting. At each consultation, the physician is duty-bound to record a detailed history from which essential knowledge of the case history may be obtained. Such information should include family history of cancer; the experience of late menopause; occurrence of profuse and irregular periods late in life; and the history of hyperplasia, polyps, and associated fibroids. Information concerning any of these factors may aid in the early detection of cancer.

The history of associated conditions, such as diabetes, obesity, hirsutism, or other metabolic disturbances, frequently plays a role in the early detection of malignancy in the uterus.

Thoughtful, diligent, and meticulous screening methods must be utilized. Requisite procedures in the diagnostic study of the patient include frequent Papanicolaou smears of the vaginal pool and cervix and office endometrial suction biopsy. These studies have a high degree of reliability when interpreted by an experienced cytologist. They are easily performed by a trained physician, without discomfort to the patient, without side effects, and without untoward symptoms or physical signs.

Such biopsies are not prone to invite lymphatic

or vascular dissemination. The excellence of the slides is most surprising. The observance of atypical cells is of considerable importance and should be followed by thorough investigation.

Much has been written on the various degrees of hyperplasia, where the cellular patterns may change from a benign to a malignant lesion. During the past years, several such cases came to our attention. Our pathologist would classify them as atypical hyperplasia—not distinguishable as either benign or malignant.

There may not be certain criteria as to when a lesion assumes a malignant change. Here, fractional dilation and curettage must be employed and may need to be repeated. Further, multiple-cell blocks of the endometrium should be reviewed microscopically until a positive diagnosis is reached.

In our clinic, 2 such cases were treated with progesterone therapy for several weeks, after which the patients underwent total hysterectomies. Postoperative microscopic studies of the endometrium revealed normal cellular histology. The question arises as to whether these patients should have been operated on or whether progesterone therapy should have been followed at intervals by diagnostic curettage.

Again, from a specimen of the suction curette, our pathologist was able to furnish a positive diagnosis of endometrial carcinoma in situ. According to the work of Kistner,² the lesion also should respond to progesterone therapy. As suggested previously, however, we believe the treatment should be definitive.

We agree that under the influence of progesterone therapy cellular patterns may be changed. We have tried this also in an occasional well-advanced lesion, with multiple spread, in order to study the effects of these drugs, but we have not been impressed by any clinical signs of improvement. Likewise, cellular patterns can be changed by cyclic desquamation³ or by curettage, but, in these unusual pathologic situations, the employment of the more energetic therapy must be kept in mind.

CHOICE OF TREATMENT

After confirming the diagnosis of adenocarcinoma of the fundus of the uterus, the selection of

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therapy definitely must be individualized. The following factors must be given consideration.

1. *Age of patient.* A 60-year-old woman should be given different consideration from one of 80 years who may be debilitated or have signs of serious systemic disease. In the elderly patient, the lesion is less likely to be highly anaplastic.

2. *Duration of symptoms.* Many patients consult their physicians within a few months, while others neglect important symptoms for a long period. The latter patients, when observed for the first time, may present evidence of widespread disease.

3. *Size of uterus and extent of the disease.* Careful consideration must be given to the surgical removal of a uterus which is movable and only minimally enlarged and where there is no extension of the disease in adjacent organs or tissues. Here, fractional curettage and examination under anesthesia may furnish an index as to extension into the myometrium or spread in the parametrium.

4. *Histologic grading of the tumor.* The tumors may be classified histologically into grades I to IV, as suggested by Broders.⁴ Grade I is the least malignant, with about 25 per cent undifferentiated cells, while grade IV is the most malignant, with 75 to 100 per cent undifferentiated cells. Irradiation usually is more effective in the highly anaplastic cell.

5. *Operability of the patient.* After pathologic confirmation of the diagnosis, a complete medical examination is undertaken to classify the medical operability of the patient. Our investigation includes intravenous pyelogram, barium enemas, proctoscopic observations, blood studies, chest roentgenogram, electrocardiogram, and any other procedure deemed necessary according to the history and physical examination. On the basis of these studies, patients are classified as (1) clinically operable, including those having no contraindications to surgery; (2) technically operable, including those having associated diseases which may alter the successful outcome of surgery; and (3) inoperable, including those patients in whom the disease is too far advanced for any type of operation.

6. *Location of the site of the lesion.* If the location, as determined by fractional curettage, is at or near the internal os of the cervix, the case should be treated more like a cervical lesion than should one located in the endometrial cavity near the cornu of the uterus. More will be said about this in relation to the choice of treatment.

In our practice, for private as well as service patients, the choice of treatment for adenocarci-

noma of the fundus is preoperative irradiation with radium followed in six weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy. The intrauterine application of radium has varied, with the use of 1, 2, or 3 capsules in tandem or the packing of the uterine cavity with multiple capsules after the technic of Heymen. In recent years, the latter method seems to have given the most favorable end results. The total dosage varies from 4,000 to 5,000 mg. an hour; occasionally, higher dosage may be used.

There should be concern about lesions located at or near the internal os. Frequently, the extension of such lesions closely resembles the spread of carcinoma of the cervix. Therefore, the irradiation approach to such a lesion should resemble the treatment of carcinoma of the cervix. Here we may resort to the Ernst applicator which permits uterine, cervical, and vaginal distribution of the radium, thus giving a more effective application to the affected areas than would be obtained by uterine application alone.

Along with many others,⁵ we believe that devitalization of the tumor cells is important and that irradiation prevents metastasis and local recurrence, promotes fibrosis, and seals lymphatic glands. This seems to reduce uterine size and, we believe, facilitates surgical technic when hysterectomy is performed six weeks later.

We concede that radium affects only a limited area, that its effect diminishes from its central source, that several types of applicators are required, and that it is more expensive and time consuming. These disadvantages, however, are minimal in comparison with the beneficial effects obtained.

We have not followed removal of the uterine body with study of multiple serial sections, as many surgeons have done, but it has been gratifying to note the low incidence of residual carcinoma in our routine laboratory examinations. The harmful effects from the use of radium have been limited to mild cystitis or proctitis.

Our surgical technic is that employed for total abdominal hysterectomy, with closure of the cervix with sutures and clamping the tubes at the cornual junction of the uterus. There is no undue manipulation of the pelvic organs. Wide excision of the parametrium and a generous excision of the upper portion of the vaginal cuff is done. Operation alone has been employed in our hospital on private patients. In this group, there are patients for whom the diagnosis was confirmed only after operation. Other patients had a short clinical history and minimal involvement and were ideal for any type of treatment. However,

the consensus in our group is that the treatment first described is preferable.

In the last few years, with the pendulum of opinion swinging toward radical operation with glandular resection in cases of cervical carcinoma, we have performed lymphadenectomy on a few patients with adenocarcinoma of the fundus in whom the lesion was at or near the internal cervical os. Our experience is limited in this area, but it is our belief that if the glands are positive, the prognosis is extremely grave. Before this method of treatment is chosen, the surgeon would prefer the uterine body to be only moderately enlarged and movable; in other words, operation is most effective before metastasis occurs. Even the most radical dissection may fail in the complete removal of all potential sites of extension. It has been the experience of many surgeons that, when pelvic nodes were found to be positive, the patients died within

one or two years. In our limited experience, we feel this is also true of cervical cancer.

SUMMARY

As physicians, we must alert our patients to recognize the early symptoms of pelvic malignancies and school them to obtain immediate medical care. We are duty-bound to obtain a detailed history and to perform a complete and thorough physical examination, including a careful investigation and meticulous screening, so that an intelligent diagnosis can be made. Treatment must then be individualized. Our first choice is irradiation with radium, followed in six weeks by total abdominal hysterectomy with bilateral salpingo-oophorectomy.

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CHILDREN with nonsuppurative otitis media or myringitis given conservative symptomatic treatment have quicker relief of symptoms than children receiving antibiotics. Also, the cure rate and the time needed for complete cure are the same with either regimen.

Conservative measures include local application of heat, using a heating pad or hot water bag, and aural instillations of a nonirritating desiccant-decongestant preparation consisting of a highly purified glycerol combined with small quantities of antipyrine and benzocaine. When pain is intense, aspirin is given every four hours until discomfort subsides. The child should be examined daily, and, if the infection does not begin to resolve after twenty-four to forty-eight hours or a suppurative complication appears, antibiotic therapy should be started. When daily observation is impossible, antibiotics in small prophylactic doses may be given in conjunction with the conservative treatment. This regimen will prevent the serious ear sequelae that have been ascribed to the indiscriminate use of large doses of antibiotics.

These conclusions are based on a study of 44 children with nonsuppurative otitis media or myringitis. Half were managed conservatively, and half were treated with locally applied heat, aspirin when necessary, and 30 mg. of tetracycline divided into 4 six-hour doses.

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The Shirodkar Procedure for Cervical Incompetence

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PROGRESS IS BEING MADE in all branches of medicine, including, of course, obstetrics and gynecology. From time to time, significant advances are brought forth which are noteworthy. A medical discovery, so to speak, that can prevent an otherwise inevitable fetal loss—a surgical operation that can save approximately 20,000 otherwise doomed babies per year in the United States alone—cannot help but attract attention.

Our discussion is centered upon the problem of cervical incompetence, with some remarks of interest on etiology, background development, and earlier reports of management. We can then proceed to a consideration of indications for surgical correction, surgical technic, choice of materials presently employed, and results that may be anticipated. It is generally agreed that the problem of early first trimester abortion is one often related to defective germ plasm and other factors largely apart from cervical incompetence. Contrariwise, however, repeated losses occurring as late abortions or early premature births are usually associated with normal-appearing fetuses and are seemingly due to an inability of the cervix to hold the pregnancy secure. It is on this particular problem that we focus our attention.

Frequently, there is history of one or more previous late abortions. Other than occasional slight spotting, bleeding is not part of the picture. Rather, the patient first becomes aware of impending loss by a feeling of unusual low pressure in the pelvis or vagina. A watery vaginal discharge is often noticed preceding the actual rupture of the bag of waters. Where there is such a significant past history, we believe that weekly examination—including vaginal palpation as well as speculum examination of the cervix—will, as the cervix loses its competence, reveal

early beginning dilation with bulge of membranes into the cervical canal. The process is silent and typically painless. Barring prompt surgical intervention or earlier prophylactic surgery, abortion becomes inevitable.

The mechanism of cervical incompetence was first described by Danforth¹ some 15 years ago. He pointed out that, as a result of congenital weakness or trauma by dilators, forceps, or other such instruments, the fibromuscular junction at the site of the anatomic internal os might be rendered insufficient to hold a growing conceptus.

Johnstone² of Melbourne has recently elucidated the hydrodynamic principles involved in the occurrence of late abortion: When the cervix is open, a bulge of membranes is created which under pressure enlarges indefinitely until either the membrane breaks or the pressure is reduced and the cervix surgically closed. The pressure at the cervix is the result of the weight of the liquid above, proportionate to its height, together with the pressure transmitted to it from the tension in the uterine wall and any positive or negative extrinsic pressure in the abdomen.

The diagnosis of incompetence may be made by the inability to pass a 6- to 8-mm. Hegar dilator through the internal os, as reported by Palmer and Lacomme³ and by Lash;⁴ by radiographic studies such as those of Rubovitz and associates,⁵ Greene-Armytage and Browne,⁶ Youssef,⁷ and Mann;⁸ or by digital exploration of the cervical canal following abortion.²

Management of the incompetent cervix falls into 2 main categories: (1) prevention by surgical attack either in the nonpregnant patient or during pregnancy before dilation begins and (2) therapeutic closure in pregnancy when the beginning abortion is recognized before the membranes herniate through the cervix and before rupture occurs.

Lash and Lash⁹ of Chicago, in 1950,—and independently Palmer³ of Brussels—were the first to write on this subject. They attempted surgical repair of the scarred cervical isthmus and suc-

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ceeded in creating a satisfactory internal os in 5 cases. Lash¹⁰ has modified his operation and continued to employ it in over 85 cases, obtaining good results in most instances. However, about one-fourth of his patients failed to conceive, and others have been disappointed with their results of this operation. Meanwhile, Shirodkar,¹¹ of Bombay, India, believing that the defect in the internal os need not be an anterior scar, carried out an encircling purse-string closure of the internal os as a therapeutic procedure during pregnancy. By 1955, he had treated 26 cases with failures in only 4. Independently, Ian McDonald¹² of Melbourne developed a similar technic of suture closure, also as a therapeutic operation. Live births with survival were obtained in 43 per cent of his patients. Where there is history of repeated late abortion, Greene-Armytage and Browne⁶ prefer to do a modified Shirodkar operation as a prophylactic procedure in early pregnancy or even before conception. They have obtained a 92 per cent success rate. In the United States, Barter and associates,¹³ also preferring nonabsorbable material such as Mersilene, have limited the operation to pregnancy after the tenth week. They carry out the Shirodkar operation when the cervix is found dilated up to 4 cm. in diameter. Also, they perform the operation in selected cases before cervical dilation has occurred. At the University of Oregon¹⁴ and at Harvard,¹⁵ nonabsorbable materials is also employed with subsequent termination of the pregnancy by cesarean section or per vaginam following division of the closure material. Success has been achieved in 70 to 90 per cent of their cases.

Our objectives are twofold. First of all, the cervix must be securely closed to hold the pregnancy to the birth of a viable infant. Our second objective is the creation of a replacing circular, fibrous, connective-tissue scar which will produce a more or less permanently competent cervix. Accordingly, we have, in all but 2 cases, employed preserved ox fascia as a means of accomplishing these dual objectives. In previous reports^{16,17} we were successful in 83 per cent of cases, a figure comparable to those where Mersilene or nylon was employed. Subsequent studies have shown good competence in 4 of 14 patients tested two or more months postpartum.

SELECTION OF CASES

The modified Shirodkar procedure has been performed in this, as well as the earlier series, in 2 groups of patients as either a prophylactic or therapeutic operation. Where there is history of late abortion losses in at least the last 2 con-

secutive pregnancies, the operation is electively carried out one or two weeks before a time corresponding to the earliest previous loss. Women who have lost fetuses qualify, we feel, only if they present a typical history. Moreover, the current pregnancy must not be complicated by appreciable early trimester bleeding.

Patients under consideration for a therapeutic operation are those giving history of only one silent late abortion or, if more than one, with an abortion and intervening viable births. Such patients are examined at weekly intervals beginning at about the sixteenth week of gestation. The cervix is carefully examined both by speculum and digital palpation for evidence of dilation, usually accompanied by effacement. Once such a change is noted, the patient is immediately admitted to the hospital and surgery is usually performed that same day.

In this series of 29 patients, the prophylactic operation was performed 19 times and the therapeutic operation 14 times. In one instance the patient was not pregnant, although she has since become pregnant and has delivered at 38 weeks. In 3 instances, a therapeutic operation was repeated later in the same gestation, and in one case a therapeutic operation was required two weeks after a failed prophylactic operation.

SURGICAL MANAGEMENT

The surgical technic is relatively simple and is surprisingly free of hemorrhage. Not one of our patients required transfusion. Likewise, despite a bulge of membranes in nearly half our patients and considerable manipulation of the cervix in all, not one pregnancy was lost through inadvertent rupture of the membranes or traumatic initiation of labor.

The patient is prepared for surgery just as in preparation for repair of cystocele. Antibiotics and progesterone (400 mg.) are usually administered parenterally the night before the operation. We have employed general anesthesia in all cases. This, together with good vaginal retraction, facilitates performance of the operation with minimal trauma to the gravid uterus. In the event the cervix is found dilated, the patient is placed in deep Trendelenburg position. The bulging bag of waters is literally pushed back up behind the internal os.

The anterior lip of the cervix is grasped with sponge forceps and drawn down. Anterior vaginal wall mucosa at the level of the bladder attachment is grasped by an Allis clamp and divided (fig. 1A). The bladder is dissected upwards. In turn, a similar mucosal cut is made posteriorly, also at the level of the internal os.

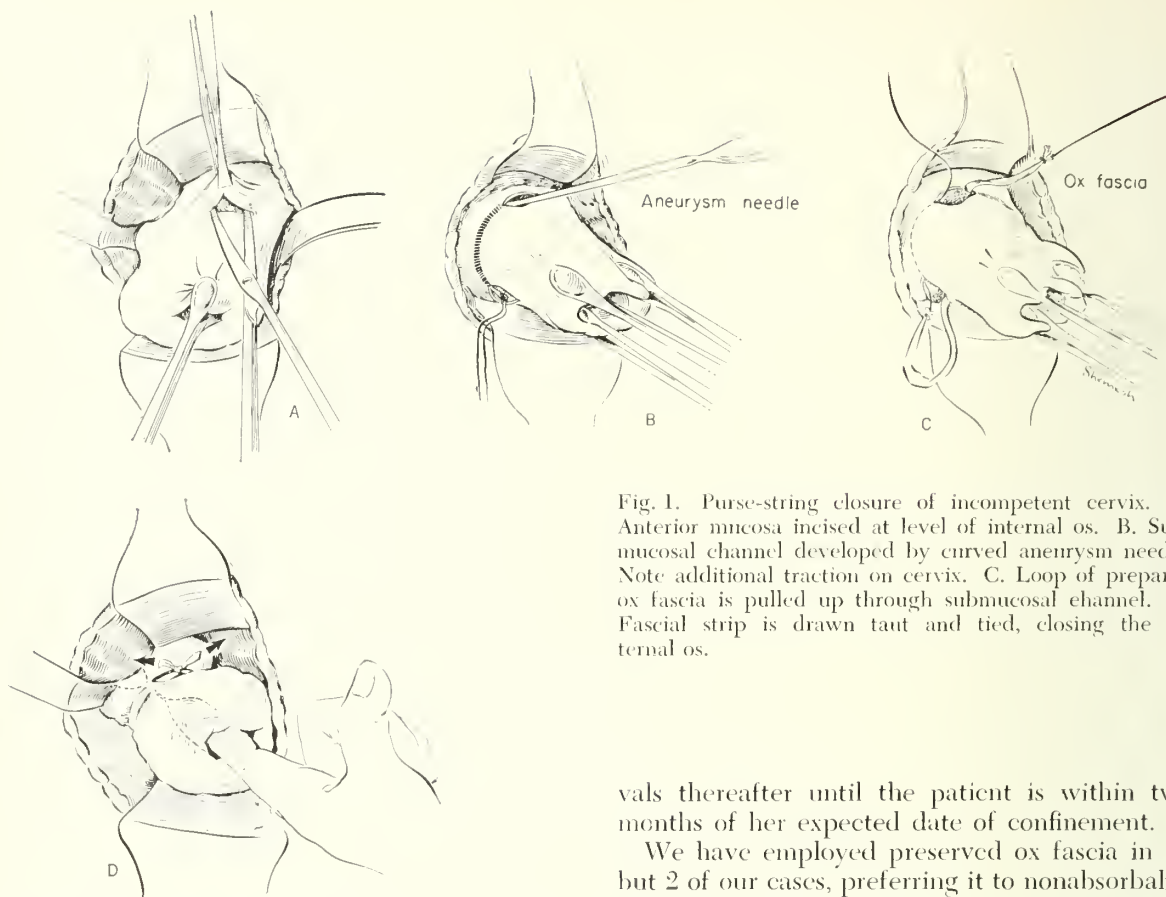


Fig. 1. Purse-string closure of incompetent cervix. A. Anterior mucosa incised at level of internal os. B. Submucosal channel developed by curved aneurysm needle. Note additional traction on cervix. C. Loop of prepared ox fascia is pulled up through submucosal channel. D. Fascial strip is drawn taut and tied, closing the internal os.

Additional traction is exerted on the cervix laterally, and submucosal channels are developed on each side using a curved aneurysm needle (fig. 1B). Medium black silk sutures replace the needle and are attached posteriorly to the free ends of a strip of prepared ox fascia. A loop of fascia, thus formed, is then drawn up through the submucosal channels (fig. 1C). Aided by digital palpation of the cervical canal, the fascial strip is drawn tight to close off the cervix at the level of the internal os and then securely tied (fig. 1D). The anterior knot and the fascia posteriorly are separately transfixed to the cervix at this level, using free silk. The anterior and posterior mucosal defects are closed with continuous triple 0 chromic catgut.

Postoperative care of the prophylactic operation is simple. Antibiotics and massive doses of progesterone are continued for three or four days. Contrary to the prolonged bed rest advocated by many, we allow our patients to get up on the second or third day and discharge them by the tenth day. The patient is advised thereafter to avoid strenuous activity and refrain from coitus. The cervix is examined at the time of discharge, one week later, and at frequent inter-

vals thereafter until the patient is within two months of her expected date of confinement.

We have employed preserved ox fascia in all but 2 of our cases, preferring it to nonabsorbable material. It handles well and stays secure as a flat band about the cervix. We believe that in time it is replaced by circular, fibrous, connective-tissue scar which maintains a competent cervix, in most cases, until term and yet allows vaginal delivery.

Vaginal delivery is permitted at or near term, and labor may be expected to proceed in the usual manner. Inasmuch as absorbable closure material is employed, division of the ox fascia has not been required nor in all probability could it be identified, as it has presumably long since been replaced by fibrous connective tissue. In one patient where Teflon was employed, the knot was excised at thirty-nine weeks with spontaneous vaginal delivery occurring the following day. We have similar plans for delivery in another patient, currently pregnant at thirty-three weeks, in whom Dacron was used.

RESULTS

The modified Shirodkar operation has been employed in 29 carefully chosen cases as summarized in table 1. Among this group, 112 pregnancies occurred before operation, with only 19 viable births (17 per cent). Of the 93 losses, 80 occurred as late abortions or previable premature

TABLE 1
SUMMARY OF CASES

Number of cases	29
Number of pregnancies	34
Age span	23-42 yr. Av., 31 yr.
Gravidity span	3-7 yr. Av., 4.4 yr.
Previous pregnancies	112
Previous losses	93 (83%)
Previous late losses	80
Previous viable births	19 (17%)

births. In only 7 cases was there evidence of any previous trauma.

We have carried out the cervical closure operation on 33 occasions. In 4 instances it was necessary to repeat the operation during the same pregnancy. Prophylactic surgery was performed 19 times, therapeutic surgery 14 times. In only one instance was the Shirodkar operation performed in a nonpregnant patient.

Infants were stillborn in only 5 of 34 women having the operation. Of the 34, 4 were successful repeated pregnancies. Successes followed previous failures in 2 patients, 1 after an unsuccessful Lash operation and the other after an unsuccessful Shirodkar operation. Five patients are currently pregnant from 4 to 17 weeks since operation. All have good cervical competence and good prospects of carrying to viability. The results are summarized in table 2.

Delivery has been per vaginam in all but 2 instances. Elective cesarean section was performed in our first patient with the misconception that vaginal delivery would not be feasible after the cervical closure operation. This patient became pregnant the following year and delivered vaginally without mishap. Cesarean section was elected in the other case because of previous unification operation involving the entire corpus of the uterus.

The route and method of delivery at term are matters of considerable importance, not only be-

cause of the concern for delivery of a viable infant but also because of future pregnancies. We favor vaginal delivery. Preferring absorbable closure material, we have found that labor will proceed in the usual manner without complication of cervical dystocia. It has been argued that, by permitting vaginal delivery, the cervical competence will have been destroyed for future pregnancies. On the basis of postpartum studies carried out on 14 of our patients, we are not prepared to accept this statement as one of actual fact. Even, however, if this should be true, repeat operations pose no special problems and certainly cannot be compared in magnitude or risk to cesarean section and repeat pregnancy thereafter. Evidently in agreement with this point of view, Easterday and Reid,¹⁵ utilizing nonabsorbable closure material, have preferred to divide the polyethylene suture at the time of labor in order to allow vaginal delivery.

Contrariwise, Barter and associates,¹³ Durfee,¹⁴ and others prefer elective cesarean section in order to preserve the permanent repair of the cervix.

SUMMARY

Repeated late abortion is a not infrequent clinical entity. In many instances it is due to mechanical factors. Of major importance is cervical incompetence of either congenital or traumatic origin.

The objectives of surgical management are twofold: (1) closure of the inadequate internal os to hold the pregnancy to viability and (2) creation of a replacing scar with which to effect a permanently competent cervix. The surgical technic is that of a relatively simple purse-string submucosal closure placed at the level of the internal os. Where absorbable ox fascia is used, unimpeded vaginal delivery can be anticipated without need for division of the suture material. Where nonabsorbable material is used, delivery may be elected either by cesarean section or per vaginam following division of the purse-string closure.

Application of the modified Shirodkar operation has been, and should be, carefully restricted to 2 groups of patients, namely, those giving history of repetitive and successive late abortions and those with the cervix found partially dilated but with membranes intact before the thirtieth week of gestation.

Our experience to date is with 29 patients (34 pregnancies) fulfilling the above requirements. The closure operation was electively performed 19 times and therapeutically performed 14 times. Repeat operation was required on 4 occasions in

TABLE 2

SUMMARY OF RESULTS FOLLOWING SURGICAL TREATMENT

Successful outcome	24
Currently pregnant	5
Failure with late abortions	5 (15%)
19 cases prophylactic operation*	3 failures
14 cases therapeutic operation	4 failures
4 cases repeat operation	2 failures
4 cases successful repeated pregnancies	
2 cases successful following previous failures	

*After 2 or more consecutive late abortions

our earlier experience but has not been required in the last 11 patients. Successful results have been achieved in all but 5 pregnancies, and 5 others are currently pregnant and nearing term. There have been 5 failures in our series of 34 pregnancies (15 per cent), as contrasted by 93 losses in 112 previous pregnancies (83 per cent).

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BRACHIAL ARTERIOGRAPHY can identify digital arteritis in arthritic patients whose hands apparently are unaffected and who have no unusual reactive hyperemia. Any artery in the hand or fingers may be affected, although blood supply of the thumb is less frequently altered than that of the fingers.

Of 11 subjects over 40 years old, 9 of them men, agglutination tests gave positive results in all. Subcutaneous nodules were found in 9, but ischemic lesions in only 7 and abnormal reactive hyperemia in only 5. Arteriograms showed irregular, narrow, or obliterated lumina, with occasional opening of collateral vessels. Poststenotic dilation or arterial dilation near bone erosions, previously reported, did not appear.

Histologic examination of digital arteries suggested intermittent, progressive collagen increase in the intima, with reduction of lumen, sometimes followed by total thrombotic occlusion. Elastic interruption did not usually cover a large segment of the vessel. In some patients, previous adventitial reaction was indicated by hemosiderin deposits around the external elastic lamina and capillaries within the media. Visceral arteries of some patients showed both slight obliterative endarteritis and, in other places, acute inflammatory arthritis. Possibly, acute polyarteritis nodosa may lead distally to obliterative changes. Though most patients had received corticosteroids for four months to four years, 2 had taken none; in a third, ischemic changes preceded steroid therapy.

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Progestin Therapy with Dydrogesterone

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SINCE October 1960, controlled observations have been made in the Department of Obstetrics and Gynecology at Ohio State University on an increasing number of patients receiving progestin for a variety of conditions. Extensive preliminary investigations had been made before the studies were initiated. In no instance did treatment appear to be a new application of progestin. The agent used was dydrogesterone (Duphaston) which is known chemically as 9-beta, 10 alpha-pregna-4, 6-diene, 3, 20-dione. The first investigation into the basic metabolic and pharmacologic activities of the drug was made by Reerink¹ and Scholer.² Additional reports have been made by Tillinger, Diczfalusy, and their associates.^{3,4}

This summary contains the observations on 61 patients. The number of patients in each of the clinical entities studied are as follows:

Endometriosis	13
Poor obstetric history and threatened abortion	13
Dysmenorrhea	7
Menometrorrhagia or irregular menses	8
Infertility	18
Amenorrhea	2
	—
	61

ENDOMETRIOSIS

Diagnosis of endometriosis was originally proved surgically in all 13 patients with this condition. Surgical removal of endometriomas was required in 2 patients. In 1 of these, a 4-cm. endometrioma was removed, but no other endometriosis was found in the pelvis. The second patient had tubes, ovaries, and uterus removed as well as an endometrioma. No other implants were found in the surgical specimens.

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Infertility was a concomitant factor in 10 of the 13 patients. At the present time, 3 of these 10 patients are pregnant and a fourth patient has been delivered of a normal male infant. All were receiving dydrogesterone at the time of conception. Dysmenorrhea in the patients who did not become pregnant has uniformly diminished and each has experienced a subjective sensation of improved well-being.

Dydrogesterone appeared to have little if any thermogenic quality. Basal body temperatures were not affected by treatment. In each instance the curve on the basal body temperature graph was monophasic, even when a constant daily dosage averaging 20 mg. of dydrogesterone was given throughout the cycle. Each graph revealed a normal, ovulatory rise.

POOR OBSTETRIC HISTORY AND THREATENED ABORTION

Of the 13 patients with poor obstetric history and threatened abortion, only 1 has failed to carry pregnancy to a viable period while receiving progestin therapy. If vaginal cytologic studies are carried on routinely during the course of a pregnancy, the outcome of the pregnancy can be predicted. When normal pregnancy cells were absent, the patient eventually aborted.

If the placenta is capable of maintaining itself, it can be supported by extraplacental progesterone. However, if the placenta is abnormal as a result of a blighted ovum, extraplacental progesterone will be of no avail for the pregnancy. To maintain a blighted ovum in the uterus would be unfortunate. Dydrogesterone will not maintain such an ovum.

DYSMENORRHEA

The 7 patients with dysmenorrhea were given 10 to 20 mg. of dydrogesterone daily from the fifth to the twenty-fifth day of the cycle. After treatment 5 patients were improved. Some were enthusiastic about the relief obtained from pain. Two patients obtained no relief, possibly because dosage was too low. The drug was well tolerated by all the patients.

MENOMETRORRHAGIA OR IRREGULAR MENSES

Cyclic therapy was given to 8 patients with irregular menstruation. Some required priming of the uterus with estrogen in the first twenty-one days of their cycles, with an overlap with dydrogesterone of fourteen to twenty-eight days. The treatment was uniformly successful with the return of all patients to a normal type of menstrual period. One patient became pregnant during treatment.

INFERTILITY

Of 18 patients with infertility, 1 had bilateral tubal blockage. In 3 other cases the husband was found to be the prime factor. The remaining 14 patients are being given dydrogesterone cyclically to enhance fertility and to attempt the rebound fertility of cyclic management. One patient became pregnant while treatment was in progress and has delivered a normal male infant. Another patient is currently pregnant.

AMENORRHEA

Dydrogesterone was found to be a normal type of replacement progesterone for the 2 patients with amenorrhea. First the uterus must be primed with estrogen. Dydrogesterone appears to be effective when the uterus is capable of response.

DISCUSSION

In these studies, dydrogesterone has been found to be an effective progestin that is well tolerated in doses as high as 120 mg. per day.

Among the 61 patients receiving dydrogesterone, 12 have been delivered of healthy infants and 4 others have become pregnant. Of these 16 patients, 12 became pregnant during treatment. The infants born include 5 females, none of whom have evidence of virilization or abnormality. No obstetric complications have occurred. Bleeding at the time of delivery has not been excessive. The 4 gravid patients are proceeding with what, from vaginal cytologic studies, appear to be normal pregnancies.

One patient receiving dydrogesterone reported a temporary acne which subsided without discontinuing treatment. Observation over an eight-

month period during which the patient received 30 mg. of dydrogesterone daily failed to reveal any adverse skin reaction.

CONCLUSIONS

1. Progestin therapy can be effectively carried out with dydrogesterone. In the 61 patients who have been receiving this treatment, 16 have either delivered or are proceeding with what appear to be normal pregnancies according to de Neef cytology. All of the deliveries have been uncomplicated.

2. If vaginal cytologic studies reveal absence of normal pregnancy cells during pregnancy, the patient can be expected to abort. Progesterone therapy in the form of dydrogesterone will not maintain a blighted ovum within the uterus.

3. Dydrogesterone has little or no thermogenic quality. Basal body temperature curves are monophasic in patients receiving constant daily doses. The graphs reveal a normal, ovulatory rise.

4. Response to dydrogesterone is variable in patients with dysmenorrhea. Some patients receive considerable relief from pain, others do not.

5. In patients with irregular menses, menometrorrhagia, and amenorrhea, dydrogesterone is of definite aid in regulating the menstrual cycle. If the uterus is capable of response, the patient is returned to a normal menstrual period.

A preliminary report of this investigation was presented at the First International Congress of Endocrinology, Copenhagen, 1960.

Duphaston (dydrogesterone, formerly known as isopregnenone) was supplied by Philips Roxane, Inc., Columbus, Ohio.

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Prescalene Fat Pad Biopsy

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SINCE Daniels¹ presentation of prescalene fat pad biopsy in 1949, several series have been published which have confirmed its value as an aid in diagnosing some intrathoracic diseases. A brief review of the literature reveals 3,041 such cases,²⁻⁵ with an over-all positive result rate of 35.8 per cent, the maximum rate being for sarcoidosis (79.8 per cent).

In general, prescalene fat pad biopsy is used for 2 different purposes:⁶ (1) as an additional procedure for diagnosing intrathoracic lesions when conventional methods of diagnosis have failed and (2) as a criterion for the operability of bronchogenic carcinoma. The primary tumor is considered inoperable⁷ when a positive result—namely, metastatic involvement of the prescalene lymph nodes—is noted, although Bansmer and associates² recognize some exceptions to this general rule. According to these authors, severe bleeding or abscess distal to neoplasm or low-grade malignancy with little involvement of the nodes should not preclude definitive surgery. The rate of involvement of the prescalene nodes in bronchogenic carcinoma, reported by various authors,^{2,3,5} varies between 8.5 and 60 per cent.³ This wide range illustrates that patients with carcinoma of the lung seek medical aid at different periods during the evolution of their disease.

Information concerning the involvement of prescalene nodes in pulmonary tuberculosis is sparse. Smith and associates⁹ report 13 cases, with 4 positive results (31 per cent). The present study was undertaken to see how frequently the prescalene nodes were involved in tuberculous patients, if this involvement was associated with special clinical forms of the disease, and whether prescalene fat pad biopsy has a practical value as an aid in the diagnosis of pulmonary tuberculosis.

MATERIAL AND METHODS

Twenty-four patients—2 men and 22 women ranging in age from 11 to 65 years, the average

age being 35.8 years—without clinically palpable nodes were subjected to prescalene fat pad biopsy at the Department of Phthisiology at the University of Istanbul. This series included patients whose disease could not be diagnosed by ordinary methods, as well as those who were clinically and bacteriologically classified as having pulmonary tuberculosis. Pertinent clinical information concerning these patients is given in the table. The side of the biopsy was chosen according to Rouvière's¹⁰ description of the pulmonary lymphatic system; left-sided biopsy was performed only for lesions involving the left upper lobe and right-sided biopsy was done both for lesions of the left lower lobe and for lesions of the right lung. The results were considered positive for tuberculosis if epithelioid cell proliferation and caseation or tubercle formation were noted on histologic examination of the lymph nodes that were removed.

RESULTS

The 24 patients subjected to prescalene fat pad biopsy were grouped as follows: 16 with pulmonary tuberculosis, 5 with bronchogenic carcinoma, 2 with sarcoidosis, and 1 with Hodgkin's disease. In 7 of these patients (cases 1, 4, 5, 6, 7, 8, 17), the procedure gave negative results (29 per cent), 6 of these being in patients with pulmonary tuberculosis and 1 in a patient with bronchogenic carcinoma.

Of 16 patients (cases 1 to 16) in whom a diagnosis of pulmonary tuberculosis was established or suspected by clinical or bronchologic examination, 10, or 62.5 per cent, showed involvement of the prescalene lymph nodes. Nine of these patients (cases 2, 9 to 16) were diagnosed solely by scalene node biopsy after other diagnostic methods had failed. These were repeated smears of sputum for acid-fast bacilli, sputum cultures for tubercle bacilli, smears and cultures from bronchial washings, and histologic examination of specimens obtained by bronchoscopic biopsy. Positive diagnosis by bronchial aspiration and/or biopsy in the same group was made in only 5 of 13 cases.

There were 13 patients with the clinical diagnosis of bi- or unilateral hilar adenopathy (cases

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CLINICAL DATA CONCERNING PATIENTS SUBJECTED TO PRESCALENE FAT PAD BIOPSY

<i>Cases</i>	<i>Age</i>	<i>Clinical and radiologic presumptive diagnosis</i>	<i>Bronchoscopy and bronchial biopsy</i>	<i>Culture and/or cytology in bronchial aspiration</i>	<i>Scalene node biopsy</i>
1	30	Right caseous tuberculosis		negative; tuberculosis in lung biopsy	negative
2	32	Right upper lobitis	negative	negative	positive: tuberculosis
3	11	Right epituberculosis		negative	positive: tuberculosis
4	25	Bilateral cavitory tuberculosis		positive: tuberculosis	negative
5	49	Right fibroulcerative tuberculosis		positive: tuberculosis	negative
6	35	Intrapulmonary lymph node perforation	positive: tuberculosis		negative
7	22	Right hilar adenopathy with bronchogenic dissemination	positive: tuberculosis	negative	negative
8	18	Bilateral hilar adenopathy	negative	positive: tuberculosis	negative
9	26	Bilateral hilar adenopathy			positive: tuberculosis
10	25	Right hilar adenopathy	negative	negative	positive: tuberculosis
11	23	Bilateral hilar adenopathy	negative		positive: tuberculosis
12	30	Left hilar adenopathy with bronchogenic dissemination		negative	positive: tuberculosis
13	44	Bilateral hilar adenopathy	negative	negative	positive: tuberculosis
14	39	Right hilar adenopathy and pulmonary infiltration	negative	negative	positive: tuberculosis
15	43	Bilateral hilar adenopathy			positive: tuberculosis
16	49	Bilateral hilar adenopathy and pulmonary infiltration	negative		positive: tuberculosis
17	45	Right opaque lung (Ca?)			negative; Ca in autopsy
18	65	Bilateral pneumonitis	negative	negative	positive: carcinoma
19	50	Right pulmonary abscess		negative	positive: carcinoma
20	43	Miliary carcinoma	positive: carcinoma	positive: carcinoma	positive: carcinoma
21	65	Macronodular pulmonary infiltration	positive: carcinoma		positive: carcinoma
22	32	Bilateral hilar adenopathy			positive: Hodgkin's disease
23	25	Bilateral hilar adenopathy			positive: sarcoidosis
24	33	Bilateral hilar adenopathy	negative		positive: sarcoidosis

7 to 16, 22 to 24), of whom only 2 with proved pulmonary tuberculosis did not show sealene node involvement (cases 7 and 8). Of the 13, 10 had pulmonary tuberculosis, proved by sealene node biopsy alone in 8 cases (cases 9 to 16); 2 had sarcoidosis, both giving positive biopsy results (cases 23 and 24); and 1 had Hodgkin's disease, with sealene node involvement (case 22).

Of the 9 patients with hilar adenopathy in whom bronchoscopic examination was carried out, only 2 gave diagnostic results (cases 7 and 8); 1 patient (case 24) was considered to have tuberculous adenopathy until sealene node biopsy revealed sarcoidosis as the true disease. On the other hand, in 6 cases, diagnosis of pulmonary tuberculosis was obtained by clinical examination when sealene node biopsy failed to reveal any lesion (cases 1, 4 to 8).

Of the 5 patients with bronchogenic carcinoma subjected to pre-scalene fat pad biopsy, results were negative in only 1 (case 17).

CONCLUSIONS

From the foregoing discussion, the following conclusions seem justified.

Pre-scalene fat pad biopsy is a valuable adjunct for diagnosing some intrathoracic lesions. Particularly in patients classified clinically as having hilar adenopathy, involvement of this group of nodes appears to be very high (84 per cent). In sarcoidosis and tuberculosis, the procedure has an established value in revealing the true nature of these lesions.

Biopsy results in other forms of pulmonary tuberculosis are not so helpful. Therefore, in the diagnosis of pulmonary tuberculosis, the procedure will prove to be of value if (1) it is confined to cases with the clinical appearance of hilar adenopathy or (2) it is used for differentiating between sarcoidosis and tuberculosis, as in

both of these groups the percentage of sealene node involvement seems to be high.

SUMMARY

1. A group of 24 patients with intrathoracic lesions—16 with pulmonary tuberculosis, 5 with bronchogenic carcinoma, 2 with sarcoidosis, and 1 with Hodgkin's disease—was subjected to pre-scalene fat pad biopsy.

2. In 16 tuberculous patients, 10 biopsies gave positive results, 8 of them being in patients with the clinical diagnosis of hilar adenopathy in whom the tuberculous nature of the lesion was revealed only by sealene node biopsy.

3. Of 5 cases of bronchogenic carcinoma, 4 showed sealene node involvement. In 2 cases of sarcoidosis and 1 case of Hodgkin's disease, biopsy results were positive.

4. Pre-scalene fat pad biopsy has definitive value in the diagnosis of cases classified as hilar adenopathy and particularly in differentiating between sarcoidosis and tuberculosis.

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MEDICAL GRAND ROUNDS

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The Kidney and Erythropoiesis

With Special Consideration of the Anemia of Chronic Renal Disease

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SINCE it first became recognized that the production and destruction of erythrocytes are a constant process, there has been much speculation and investigation of the mechanisms behind the phenomenon of erythropoiesis. It has long been known that adaptation to high altitudes and congenital cyanotic heart disease were associated with polycythemia and therefore it was only natural that hypoxemia should be considered the primary stimulus for the increased formation of red blood cells in such conditions. Until relatively recent years, hypoxemia was thought by most authorities to be the sole factor regulating erythropoiesis.

Not until the past decade has there been any great progress in the solution of this problem, in spite of the fact that the presence of a circulating humoral erythropoietic factor was postulated over half a century ago. In 1906, Carnot and Deflandre¹ injected serum of rabbits bled twenty hours previously into normal rabbits and observed an increase of 1.5 million red blood cells per cubic milliliter in the recipient animals within one to three days. The marrow of these animals was hyperplastic with an increase in normoblasts, and many small erythrocytes were noted. Carnot introduced the term, "hemopoietin" to designate the unknown substance in the donor serum responsible for these changes.¹

Forster, in a similar work reported in 1924, demonstrated the presence of hemopoietin in the sera of animals exposed to low oxygen tension² and in 1950, Reisman,³ in a classic experiment

using parabiotic rats, demonstrated erythropoiesis in both partners when one was exposed to gas of low oxygen content. He concluded that the stimulus for increased erythropoiesis in the partner breathing ordinary air was a humoral factor elicited by hypoxemia in the one breathing the low-oxygen gas. Erythropoiesis in this case was measured by increase in nucleated red blood cells in the marrow.

Stohlin and his associates⁴ in 1954 collected data from a patient with polycythemia secondary to a patent ductus arteriosus with reversed flow. The oxygen saturation and oxygen tension of brachial arterial blood and sternal marrow were normal, while those of the iliac marrow and femoral arterial blood were reduced. The presence of polycythemia under these circumstances excludes a primary cerebral or pituitary mechanism and the presence of hypercellularity and normoblastic hyperplasia in normally oxygenated areas of the marrow are against a direct effect of lowered oxygen content or tension on the germinal erythroid cells.

These and other observations are compatible with a humoral regulation of erythropoiesis in the hypoxic state and tend to disprove the previously accepted view that oxygen tension in blood supplying the bone marrow is the primary stimulus to erythropoiesis.

METHODS OF INVESTIGATION

Much of the work which has been done in this field involves three factors: (1) an animal in which erythropoiesis can be made to proceed at a rapid rate, (2) an animal in which erythropoiesis can be eliminated, and (3) a suitable assay method.

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Conditions resulting in increased erythropoiesis. Erythropoiesis is known to proceed at a rapid pace in animals made anemic by bleeding,⁵⁻⁹ in animals exposed to atmospheres of low oxygen content,^{3, 10-12} and in animals treated with cobalt.^{11, 13} The common denominator of all three of these conditions is probably anoxemia. This is easily seen in the first example (anemic anoxemia) and in the second (anoxic anoxemia) and is possibly true in the case of cobalt treatment.

Polycythemia in response to cobalt can be produced in all animals, including man. Although cobalt deficiency is not associated with anemia, cobalt is considered a potent erythropoietic agent.^{10, 14} Wintrobe postulates that the action of cobalt is dependent upon the inhibition of those mechanisms concerned with the transport of oxygen and the resultant tissue anoxia.¹⁵ In a similar fashion, para-aminopropiophenone (PAPP) and phenylhydrazine produce a severe though transient tissue anoxia resulting in an increase in erythropoiesis.^{16, 17} Treatment with triiodothyronine and, similarly, dinitrophenol, by producing a relative hypoxia, also increases the rate of erythropoiesis.⁷

Conditions resulting in a decreased rate of erythropoiesis. Animals subjected to hypophysectomy,^{7, 8, 18} an atmosphere of high oxygen content,¹⁸ starvation,¹⁹ and transfusion-induced polycythemia^{8, 20} all have a decreased rate of erythropoiesis. Fried and his associates believe that the rate of erythropoiesis is determined by the amount of a circulating erythropoiesis-stimulating factor or factors (ESF), the production of which is regulated by the relationship between the oxygen supply and demand and not by the supply alone. Thus bleeding and anoxia reduce the tissue oxygenation directly while, in triiodothyronine-treated animals, the supply may be unchanged but the demand increased. Similarly, animals exposed to high atmospheric oxygen or rendered polycythemic by transfusion have an increased supply of oxygen, while hypophysectomized or starved animals, though normally oxygenated, have a relative abundance of oxygen in relation to their bodies' lowered demands. Thus, it appears that the early concept of tissue anoxia producing increased blood formation is true, though the effect of anoxia is mediated through a circulating factor and is not exerted directly on the bone marrow.

Methods of assay. In the classic type of procedure for the demonstration of ESF, serum or a serum fraction from an animal in which erythropoiesis has been stimulated is injected into an

animal in which erythropoiesis is at a minimum. Stimulation (or absence of stimulation) in the recipient animal can be measured by several means. Among these are changes in hemoglobin, hematocrit,¹ circulating cell mass,²¹ increase in reticulocytosis,^{5, 6, 8, 22} or changes in bone marrow.³ Jacobson and Goldwasser⁹ have suggested that histologic observations of the spleen are also reliable indices of erythropoiesis in the rat and mouse.

A decided step forward was achieved when in 1955 Jacobson and his group published a method of bioassay of ESF, utilizing the incorporation into newly formed reticulocytes of radioactive Fe⁵⁹.²³ They found that reproducible results could be obtained by the injection of the Fe⁵⁹ solution within a few hours of the final infusion of anemic plasma and by withdrawing samples twelve hours later. The validity and usefulness of this procedure have been confirmed.^{12, 20, 24} Recently Keighley,¹⁶ working in conjunction with Goldwasser, Stohlman and others, proposed the adaptation of a tentative unit of ESF based on a net incorporation into rat red cells of 20 per cent of injected Fe⁵⁹, using a standardized assay procedure.

THE NATURE OF ESF

Though still relatively little is known of the actual nature of ESF, there are few authorities who dispute its existence. Recent interest in the field has greatly broadened our understanding of the problem.

In 1949, Chiuni, Oliva, and Tremontana,²⁵ writing on the humoral regulation of normo-erythropoiesis, reported a reticulocytosis in human beings following the infusion of 20 ml. of serum from pernicious anemia patients at peak levels of reticulocytosis following liver therapy. In 1953, Erslev's group²⁶ reported that serum from anemic monkeys produced a reticulocytosis in normal monkeys, although, in this case, large amounts of serum—in the region of 6 to 10 per cent of body weight—were required. Jacobson has recently pointed out that plasma from last trimester pregnant mice also has a high ESF activity.²⁷

It has been well established that serum from anemic animals can cause erythropoiesis in normal or polycythemic animals. More recently it has been shown that human plasma extract from patients with polycythemia vera and some secondary polycythemias is capable of stimulating erythropoiesis in normal rats. In this study, Linman and Bethell²⁸ reported increases in reticulocytes, erythrocytes, and bone marrow activity, but no increase in hemoglobin or hematocrit.

Goldwasser observed that plasma taken from normal animals ten hours after cobalt injection was equally as effective as anemic plasma in producing an increase in Fe⁵⁹ incorporation in the recipient animal.¹⁰

In a recent publication, Reichlin and Harrington²⁰ demonstrated the presence of ESF in normal rat plasma. They reported predictable response under various conditions and believe that quantitation of ESF action is possible, not only under circumstances of increased erythropoiesis, but in the normal and polycythemic as well.

Besides occurring in serum, ESF has been shown to be present in the urine of normal human beings²⁹ and in the urine of patients with aplastic anemia.³⁰ In the latter case, ESF levels were exceptionally high. A concentration of this urine equivalent to 30 cc. of whole urine, when injected daily for fourteen days, produced polycythemia in normal rats greater than that caused by simulated altitudes of 15,000 feet for an equal period. The fact that ESF may also appear in the milk was demonstrated by Grant³¹ when he reported greater levels of hematocrit, reticulocytes and oxygen capacity in the offspring of hypoxic rats than in baby rats nursed by normal mothers.

Chemistry of ESF. Barsook and associates, using rats as recipient animals, found ESF activity in a nonprotein plasma extract of rabbits which was obtained by boiling and addition of 7 per cent trichloroacetic acid.²¹ This observation was supported by Gordon but disputed by Erslev,³² who repeated the experiment, using rabbits as both donor and recipient animals and normal serum instead of saline as controls, and demonstrated no activity in such a fraction. Instead, he believes that the ESF is in serum as well as in plasma, does not dialyze through a cellophane membrane, and is present in the fraction containing alpha and beta globulins.⁶ Rambach and associates³³ are proponents of this theory and suggest that erythropoietin is a mucoprotein.

Linman's group³⁴ in 1958 reported that ESF in boiled anemic plasma was soluble in ether. On the basis of data available at that time they postulated the existence of more than one factor. One is a heat-stable and ether-soluble lipid. It was said to stimulate erythroblastic division but not hemoglobin synthesis. Another is relatively thermolabile, insoluble in ether, and probably protein in nature. It appears to augment hemoglobin production.

The currently accepted view, according to Gordon³⁵ in a recent exhaustive review, is that of Goldwasser and White³⁶ who, by the use of

3 successive ion-exchange procedures, prepared a highly active fraction from anemic sheep plasma. This material had the properties of an alpha 1 glycoprotein with a molecular weight of 40,000 and was nonanaphylactic in guinea pigs. It was fractionated further on an ion exchange resin into a large amount of alpha-1 glycoprotein and a small amount of highly active alpha-2 glycoprotein material. The possibility of an active polypeptide grouping in addition has been postulated.³⁵

Mode in action. Rambach, using the ESF activity associated with boiled filtrate of anemic rabbit plasma, showed that, when injected into the rat, this fraction produced an increase in the rate of cell division and maturation and acceleration of release from the organs of hemopoiesis.³³ Erslev,²² in a well-planned study, also investigated the cellular development of the nucleated red blood cells. Rabbits were bled, kept anemic for twenty hours, and then retransfused. The characteristic reticulocytosis was observed which continued for a few days after termination of the anemic anoxia. In this period, reticulocytosis was not suppressed by high oxygen or stimulated further by continued anemia. When mitotic division was arrested by colchicine during the period of anoxia, the reticulocyte response was delayed for twenty-four hours but was otherwise of the same magnitude. These observations are said to indicate that an anoxic stimulus operates in the bone marrow by accelerating the differentiation of stem cells into pronormoblasts and that, thereafter, further cellular divisions and maturation proceed at a fixed rate independent of the original anoxic stimulus.

The recent work of Gallagher and Lange²⁴ suggests a dual site for the action of ESF. In rats in which maximum erythroid arrest was thought to have been induced by both starvation and transfusion, ESF infusion provoked an increase in Fe⁵⁹ utilization in forty-eight hours and a reticulocyte response in seventy-two hours. In rats prepared by transfusion alone and considered to represent only partial or incomplete erythroid arrest, the response was much faster. The response in maximally arrested marrows was thought to be due to the effect on stem-cell division while the earlier response in incompletely arrested marrows was believed due to action of ESF on the more mature erythroid precursors.

The concept that ESF not only stimulates red-cell production but is consumed in the process was advanced by Stohlman.¹² He showed that erythropoiesis in normal rats exposed to simulated altitudes reached a peak in twelve to twenty-four hours and declined to nearly zero at forty-

eight hours, while rats whose red-cell production was totally suppressed by ionizing radiation showed much higher erythropoietic levels with activity remaining after ninety hours. This concept of ESF utilization may also serve to explain the observation that the level of ESF is often greater in patients with aplastic anemia than in patients with the same level of hemoglobin whose anemia is due to blood loss or hemolysis.

RELATIONSHIP OF ESF TO THE KIDNEY

The association between chronic renal disease and anemia has been an established fact for many years^{14, 37-39} and more recently attention has been drawn to the polycythemia associated with certain neoplastic renal lesions.^{19, 40} It is not unusual, therefore, that a direct association between ESF and the kidney has been postulated almost since the concept of a circulating erythropoietic factor itself was first proposed. With few exceptions, the ensuing investigative work in this field has been confirmatory.

The site of ESF production. It has been well documented that erythropoiesis can occur after anoxie stimulus or cobalt in test animals after removal of the pituitary, thyroid, spleen, gonads, adrenals, pancreas, stomach, intestine, or almost 90 per cent of the liver.^{9, 13} It has also been shown that production of the erythropoietic factor in rabbits is normal even after damage to the lymphatic and hematopoietic systems by nitrogen mustard.⁶

It has been equally well demonstrated that there is a uniform loss of erythropoietic activity in response to the usual stimuli in test animals subjected to bilateral nephrectomy.^{9, 13, 27, 41} In animals made uremic by ligation of both ureters, there is a decrease but not a complete absence of erythropoietic response.^{9, 13, 27} However, Jacobson⁹ found that the capacity to produce ESF following bilateral ureteral ligation is greater twelve hours postoperatively than at twenty-four hours, thus suggesting that the toxemia of uremia may actually suppress the production of ESF.

In a recently published report, Gurney⁴² described studies done on tissue from 2 patients with polycythemia. One of them had metastatic renal carcinoma, the other, polycystic disease of the kidney. In the latter case, test animals were given 0.6 ml. of cystic fluid from a surgically removed kidney daily for two days, and an 8-fold stimulation of Fe⁵⁹ uptake was observed as compared with saline controls. Bioassay of a tumor homogenate from the other patient demonstrated an even more striking response.

In analyzing these data, it seems fairly conclusive that the kidney is indeed the site of ESF production. Many authors, however, while agreeing to this tenet, do so not without certain reservations. Jacobson and associates,²⁷ in reporting a recent series of investigations in which very slight but measurable reticulocytosis was achieved in nephrectomized rats, felt that the possibility of a second site of ESF production outside the kidney must be considered—a situation analogous to androgen production occurring principally in the gonads but also in the adrenals.

Other alternative hypotheses include the following. Toxic conditions associated with nephrectomy may be responsible for failure of ESF production. Such toxic conditions may be greater in bilateral nephrectomy than in simple ureteral ligation.⁹ The kidney may be only one link in the manufacture of erythropoietin. Another organ may produce a precursor in response to cobalt or bleeding which is activated in the kidney, or perhaps by an anoxic kidney. Or the kidney may make an inactive precursor that is activated elsewhere.^{9, 13}

The anemia of nremia. In a study of bilaterally nephrectomized rabbits, Muirhead³⁸ found the ensuing anemia to be rapid in its development. He felt that the rapidity indicated hemolysis. This belief was further supported by the observation of increased serum bilirubin and fecal urobilinogen, increased serum iron, increased iron content of the spleen, and a normal or elevated marrow erythroid content. A relative reticulocytopenia was also observed, however. The concept of hemolytic anemia in uremia was strengthened by Sutherland's group when they studied uremics by the radio-chromium method and found lowered cell survivals in 9 out of 11 patients so studied.³⁹

Loge, Lange, and Moore³⁷ reporting their evaluation of 26 cases of uremic anemia concluded that hemolysis was not a prominent mechanism. They characterized the anemia as normocytic, normochromic with serum iron and erythrocyte protoporphyrin values following no consistent pattern and an invariable depression of erythropoiesis as demonstrated by poor utilization of Fe⁵⁹. They also found that erythrocytes formed in uremics were able to survive normally in healthy recipients. Desforges and Dawson¹⁴ in a similar analysis found hemolysis to be a common abnormality but only moderately so. They also demonstrated decrease in Fe⁵⁹ turnover in uremics.

ESF in nremia. One must therefore conclude

that, although hemolysis probably plays a part in at least some cases of uremic anemia, a decrease in the rate of erythropoiesis is probably equally and perhaps even more important.

In a study done on 16 human anemic uremic patients, Gallagher and his associates⁴³ evaluated the plasma level of ESF and demonstrated that 15 showed no action of ESF as measured by Fe⁵⁹ incorporation and 1 had only slight activity.

Erslev⁴⁴ reported a study done on normal rabbits and rabbits made uremic by unilateral nephrectomy and contralateral ureteral ligation. He demonstrated not only the failure of uremic rabbits to respond to bleeding by increased reticulocytosis and the failure of serum from uremic anemic rabbits to cause erythropoietic activity in normal subjects, but he also demonstrated the inability of uremic animals to respond with reticulocytosis to infusion of serum with known erythropoietic activity. He concluded that anemia in uremic rabbits is related to the metabolic changes associated with uremia rather than to loss of renal tissue and is associated with not only a reduced production of ESF but with a failure to respond to this factor. Desforges¹⁴ also suggested the possibility that the kidney is responsible only indirectly by failure to excrete a toxic product rather than directly by failure to produce an erythropoietic substance. She believes it "not unlikely" that both mechanisms play some part.

CONCLUSIONS

On the basis of much of the pertinent literature published within the past decade it is almost impossible to deny the existence of a circulating erythropoiesis stimulating factor or factors, the production of which is stimulated by conditions of anoxia or relative anoxia, and suppressed by polycythemia or relative polycythemia. Furthermore, one must conclude that the kidney plays a vital role in the production of this factor. Though the data thus far at hand do not allow one to draw a definite conclusion regarding the exact nature of this role it seems likely that the kidney is directly responsible for either the production or the activation of ESF and that this function is impaired in chronic renal disease and uremia.

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NEEDLE ASPIRATION of a lymph node is a simple, rapid, painless, and accurate diagnostic method. Usually, the specimen is obtained in less than thirty seconds, and the stained smear is ready for microscopic examination in minutes. Since the node remains intact, reaspiration in another portion or surgical biopsy can be done later if necessary. The index and middle fingers of the left hand hold the node in a fixed position and draw the overlying skin taut. After the skin is wiped with an alcohol sponge, a dry 20-gauge needle on a dry 5-cc. syringe is pushed into the node with a single, rapid motion. Suction is applied and held on the syringe barrel, and the needle is pulled out immediately. The aspirated fluid, which is limited to the needle, is spread on a clean glass slide and is stained with Wright's and Giemsa stains.

M. H. STICH: Lymph node aspiration. *Am. J. M. Sc.* 243:1-12, 1962.

IN PATIENTS with infectious hepatitis benefited by prednisolone, the serum bilirubin value falls rapidly during the first twenty-four to forty-eight hours and then continues to decrease at a much slower rate. In contrast, the rate of clearance is constant in patients recovering without steroid therapy. In patients with obstructive jaundice benefited by prednisolone, the fall in serum bilirubin value is less decided. The response in patients with hepatitis and obstructive jaundice cannot be attributed to increased biliary excretion, altered renal clearance of bile pigments, or decreased rate of red cell breakdown. Possibly, steroid therapy causes or enhances bilirubin excretion through an additional metabolic pathway.

R. WILLIAMS and B. H. BILLING: Action of steroid therapy in jaundice. *Lancet* 2:392-396, 1961.



Notes from a Medical Journey

Moscow, U.S.S.R.
11 September, 1961

Dear Jay:

Moscow shows many changes in five years. Driving in from the airport we went past miles of 8-story apartment buildings where there were only fields and log cabin farmhouses in 1956. Part of the way we drove on completed portions of the new superhighway to Leningrad, and in the center of the city it is obvious that Moscow has advanced to the point where it is easy to get killed by automobiles. Traffic is not really heavy by our standards, but it is fast and disorderly.

Dr. Myasnikov's Institute of Therapy is much changed too -- doubled in size and far better equipped than before. Today I gave an informal lecture to the staff with about a hundred doctors being assembled on short notice. And the atmosphere is different, less formal, and more relaxed; we actually discussed technical problems instead of being exposed to dogmatic statements. This is partly because of the fact that we know one another better from friendly meetings in Geneva, Stockholm, Brussels, and Rome in the last few years. And part of the change, I am sure, reflects the fact that the Russians now have more to offer in medical science and they know it.

One incident impressed me while going through the laboratories. Dr. Myasnikov waved at a bank of complicated equipment, said "stereovector electrocardiograph," and kept on walking. But we stopped and asked where it was made. "In Russia," said Myasnikov and started to go on. "But how do you like it?" we asked. He grinned and said, "It's no good. It doesn't work." Such an exchange would have been unthinkable in 1956.

Last night, we (Dr. Paul White, Margaret, and I) had dinner at Myasnikov's apartment with his wife, son, and daughter-in-law. The atmosphere was just like visiting friends in our own country. We talked about our colleagues, art (he has a fine collection of Russian paintings), food and drink, the complications of travel, and hunting for mushrooms.

We liked a kind of partly fermented sauerkraut, whereat the recipe was reconstructed with lively discussion and recourse to dictionaries and cook books. (You start with 50 pounds of cabbage and it is ready in 2 or 3 days.) It was that kind of an evening.

We arrived here by a Russian jet from Prague where we had attended the last two days of an International Congress on Angiology. The Czechs were most cordial and the social affairs were delightful, but we learned little from the scientific sessions. I was impressed with the Secretary General of the Congress, Prof. Z. Reinis, who seems to have an intelligent grasp of the epidemiologic approach to heart disease. Perhaps a fourth of the participants were from non-Communist countries but they were a very mixed bag, mostly men I had never heard of before (including those from the U.S.).

Prague used to be an impressive city and it is crowded enough (with pedestrians), but all seems rather down-at-heel. This last phrase comes to mind because I got to looking at shoes in shops and on the passers-by and could not believe that Czechoslovakia once had a high place in the ranks of producers of good shoes. All consumer goods seemed to be high in price and low in quality. There is no unemployment but a serious labor shortage. I would guess that part of this is the result of the great numbers of men in military service and in the police -- who are everywhere.

The current trip started ten days ago when Margaret and I flew to Ireland and got fouled up with an Irish Airlines jet that could not fly (eventually we were transferred to TWA) and bad weather. So we missed a night's sleep and had no real food from lunch on Saturday in New York until dinner late Sunday evening with Dr. Tim Counihan and his wife in Dublin.

Counihan is the new professor of medicine at University College, charming and able but so swamped with patients he will find it difficult to do any of the research in cardiology that interests him. He confirmed my suspicion that there are no reliable data on the frequency of heart disease in Ireland or on the average diet of the population. Dr. Fred Stare of Harvard has some kind of a cooperative research program going, comparing men in Ireland with their relatives in Boston, but nothing like an acceptable sample of the population has been set up.

Dublin was full of the International Congress on Surgery but we went on to Manchester the next day, after standing eight hours fogged in at the tiny airport. At Manchester, many hours late, we were met by the president of the Cooperative Insurance Society (which is building the largest skyscraper in England for its headquarters) and Prof. Jean Lequime, who had come over from Brussels to sit in on discussions about a research program which the Cooperative has agreed to sponsor. The purpose of the program is to determine the value of blood cholesterol measurements in predicting the risk of future heart attacks. We hope to get about 5,000 subjects a year, starting next spring. The big problem is to persuade 700 or so doctors to assist by putting a few drops of blood on filter paper for us. Pricking a finger is an "assault" that requires assent in England.

Manchester to Brussels is an easy direct flight and there we stayed at the Fondation Universitaire as Lequime's guests, since all hotels were full (conventions!). Lequime plans to set up a research program, under my coordination, which will cover thousands of employees of banks and other corporations in Brussels. La Prevoyance Sociale will underwrite most of the program. La Provoyance is by far the largest insurance company in Belgium and, though a cooperative, is run as a benevolent dictatorship by our friends Henri and Raymond Lemaire. Instead of cutting insurance premiums, they believe in collecting what the traffic will bear and putting the profits into good works -- hospitals, preventoria, and now research.

At Brussels we inspected Lequime's new Institute of Cardiovascular Research which will be formally opened by the Queen on the 14th (but we could not stay so long). The Institute adjoins the Departments of Medicine and Surgery on either side and is admirably equipped. It will make a fine locus for our joint research in Belgium.

Finally, Dr. Paul White flew in from Boston. We had an elegant lunch (all varieties of fish and shellfish), an hour's rest and then we were on a Czech plane bound for Prague. We were cordially greeted at the airport, and Paul was soon whisked off to the hotel. Margaret and I lacked proper visas, so we had to wait in a dismal room until 2 a.m. when, finally, a phone call released us.

Such is the restful life of a traveler. With all the best,

As ever,

A handwritten signature in dark ink, reading "Ancel Keys". The signature is fluid and cursive, with the first name "Ancel" and the last name "Keys" clearly distinguishable.

Ancel Keys

AK/ji



Walter Reeve Ramsey, M.D.

*Pioneer Pediatrician, Teacher of Pediatrics,
and Founder of the First Children's Hospital
in the Northwest*

ROBERT ROSENTHAL, M.D.

St. Paul

LIFE IS SELDOM sufficiently gracious to grant a man the fulfillment of his heart's desire. Yet, Dr. Walter Reeve Ramsey of St. Paul, Minnesota, is one of the few men to realize his dreams and hopes. Although not the first physician to teach pediatrics in the North Star State, he was the first full-time pediatrician in the area. It was he who planned and supervised the building of the Children's Hospital in St. Paul, the first institution of its kind between Chicago and the Pacific coast.

Dr. Ramsey always has taken pride in his Scotch ancestry. He speaks with affection of his kinsmen who emigrated to the northwestern wilderness in 1812, the year an infant United States was fighting its second war with England. John Smith and his wife, Dr. Ramsey's great-grandparents, settled near the Red River of the North and allied themselves with the famous colony founded by Thomas Douglas, Earl of Selkirk. The Selkirk Colony was only a year old when the Smiths arrived. They remained in the colony for four years until hostilities between the North-West Company and the Hudson's Bay Company made it necessary for them to leave. Eventually they settled at Niagara Falls. It was there that Smith's daughter, Jean, married Robert Ramsey, who was to become Dr. Ramsey's grandfather. Dr. Ramsey also takes pride in the fact that he and Minnesota's first governor, Alexander Ram-

sey, had a common ancestor, also named Alexander, and that his mother was a first cousin of the railroad builder, James Jerome Hill.

Dr. Ramsey's parents were James and Mary Scott Ramsey. He was born at Guelph, Ontario, on November 8, 1872. His early education was acquired at the Guelph Collegiate Institute, and he began the study of medicine at the University of Maryland in 1893 and completed it at the University of Minnesota Medical School from which he graduated in 1896.

The young Dr. Ramsey interned at the St. Paul City and County Hospital, later known as Aneker Hospital. At the conclusion of internship, he began his private practice in St. Paul. In 1900, he was appointed government physician for the post office and apparently was the first to hold this post. However, his interest in children's diseases soon became evident, and in the same year he was appointed to the staff of the City and County Hospital, department of diseases of children. After some postgraduate work in New York and Boston, he began his teaching career in 1901 at the University of Minnesota Medical School.

The year 1902 marked a turning point in Dr. Ramsey's personal and professional life. He married Ruth A. Lusk, daughter of Judge James Lusk, and the young couple left the same day for travel and study in Europe. For almost a year Dr. Ramsey studied in the great medical centers at Vienna and Berlin. In Vienna he was introduced to modern knowledge of urinary infections and other diseases of children at Theodore Escherich's famous clinic. In Berlin, he

ROBERT ROSENTHAL has been in private practice in pediatrics since 1924. He is clinical assistant professor of pediatrics, University of Minnesota.

worked with Adolph B. Baginski at the Charité. He became so enthusiastic and so engrossed in diseases of the young that when he returned to St. Paul he limited his practice to pediatrics. Thus he became the first full-time pediatrician in the region. He also resumed his teaching at the University of Minnesota. Several years later, in 1907 to 1908, Dr. Ramsey again returned to Germany, this time to work as assistant to Professor Johann Otto Leonhardt Heubner at the Charité.

Dr. Ramsey had an intense interest in the child. He was concerned not only with the child's diseases and their treatment but also with its general care and social welfare. It was this sweep of interest which resulted in the organization of the Baby Welfare Clinic of St. Paul, an agency which offered pediatric advice to normal children as well as those who were ill. The clinic offered its services to that large group which was not indigent but neither sufficiently well off to be able to consult private physicians. Today the clinic is a part of the Family Nursing Service of St. Paul and is devoted only to well children.

A man of vision, Dr. Ramsey realized that information concerning children was needed for use by the public. With characteristic vigor, he set about putting his knowledge into books easily understood by the layman. In 1916, he published his book *Infancy and Childhood*. The same year appeared his *Care and Feeding of Infants and Children: A Textbook for Trained Nurses*. Each became popular, and the latter appeared in several editions. His volume for nurses apparently was the first text of its kind for use in training schools for nurses in the United States.

Dr. Ramsey was very interested in infant feeding. As the result of his European experiences, he introduced buttermilk as an infant food and often read papers before the Ramsey County Medical Society extolling its virtue. On occasion he contributed articles on the subject to professional journals. Other subjects of special interest were urinary infections in infants and small children and eczema. His reflections on these also appeared in periodicals.

With such a range of interests, activities, and publications, it is little wonder that Dr. Ramsey's contributions should be recognized. He was elected to the Minnesota Academy of Medicine in 1908 and to the American Pediatric Society in 1917. He was among the organizers of the Central States Pediatric Society and the Northwestern Pediatric Society. At the University of Minnesota, he steadily advanced from clinical assistant in 1901 to 1903 to associate professor in 1916. During 1917 and 1918, he served as acting

chief of the department of pediatrics. He became emeritus professor in 1941.

World War I brought unexpected changes in Dr. Ramsey's career and, as it did so many others, carried him to new enterprises. In 1918, he offered his services to the American Red Cross, was commissioned a major and sent to France where, for eighteen months, he was in charge of the children and refugee service. As a representative of the United States Children's Bureau, Dr. Ramsey assisted the French government in the establishment of a Children's Dispensary, a Children's Hospital, and a preventorium for tuberculosis in Rouen. In grateful recognition of his services, both the French government and the city of Rouen presented him with gold medals. When the League of Red Cross Societies was organized in Cannes, Dr. Ramsey attended as a delegate.

Dr. Ramsey's war work in France was remembered in 1921 when the first World Congress for Child Welfare met in Brussels. The government of Belgium invited Ramsey to present a paper dealing with the prevention of tuberculosis in children. Dr. Ramsey was named the official delegate of the United States. After the sessions, he and Mrs. Ramsey went on to Switzerland to visit the famous clinic of Professor Auguste Rollier at Leysin. This Swiss physician specialized in the treatment of tuberculosis, especially of the glands, bones, and joints, in children. It was there that Dr. Ramsey, seeing the results obtained from exposure to the sun, conceived the idea of a children's hospital in St. Paul. Two years later, Ramsey again visited the Rollier Clinic when he was in Switzerland as his nation's delegate to the Second International Congress for Child Welfare where he again presented a paper. At Dr. Rollier's invitation, he guided surgeons who visited the clinic after attending the World Congress for Surgery in London.

Upon his return to St. Paul, Dr. Ramsey began to make his dream for a children's hospital a reality. The project had been on his mind for years. He had speculated as to the institution's location and had faced the question of proper financing. Indeed, he had purchased 5 lots on a site which he felt would be ideal—high elevation for abundant sunlight the entire year and protection against chilling winds in winter. These lots were located above Pleasant Avenue, only a block north of St. Luke's Hospital.

With a location fixed and lots purchased, Ramsey threw himself into the task of eliciting the financial support of influential citizens. A Board of Trustees was formed and a Children's Hos-

pital incorporated. While waiting for the completion of the hospital, Ramsey accepted a generous offer of St. Luke's Hospital, which gave him for temporary use an old frame building standing adjacent to the hospital. The structure was remodeled with a capacity of 16 beds. Except for the medical staff, everything—surgical facilities, kitchen, laboratory—was supplied by St. Luke's Hospital. The institution opened on January 1, 1924. Though somewhat rudimentary, this first children's hospital was a step in the right direction. Dr. Ramsey, pleased with the simple structure, loved to look at a large sign, which read: Children's Hospital, Inc. His memory holds a store of stories of the odd and unusual cases which came to be treated.

The cornerstone of the new Children's Hospital was laid in August, 1927, in the presence of a distinguished group of citizens and well-wishers. Monsignor Humphrey Moynahan offered the prayer of dedication, and Dr. Isaac Abt, of Chicago, gave the major address. A group representing the National Hospital Association was in attendance. The 3-story structure received its first patients in 1928. Dr. Ramsey held the unpaid position of medical director, and the staff consisted of 15 physicians. Indeed, the hospital was Ramsey's first love. He had personally planned much of it, and he was fond of showing visitors its broad expanse open to the sun, the modern facilities, and the attention given to small details. Dr. Ramsey visualized the institution as a center for child care, not only in St. Paul but also for the surrounding area. To him, it was to be a pediatric research center and teaching institution.

Time spent abroad and energy devoted to the Children's Hospital made it necessary for Dr. Ramsey to get help in his private practice. At first, Dr. O. E. Groebner was associated with him as his assistant. Later, Drs. George Hagan and Alexander Stewart, together with Dr. Ramsey, formed the Children's Clinic. This group continued until about 1930, when it gradually split. For a few years Dr. Ramsey continued by himself, and then he retired in 1933.

His life, indeed, was full of many things. He served as consulting health editor of *The Farmer* and *The Farmer's Wife*, both published by the Webb Publishing Company of St. Paul. The Webb Publishing Company assisted Dr. Ramsey in raising funds for needy farm children. "The Helping Hand Club" endeared him to many. For many years Ramsey served as state chairman

of the Polio Foundation; during World War II, he was chairman of the Ramsey County Medical Society's committee for the collection of instruments and drugs to be used by the Russians, then our allies; his advice and counsel was sought in a variety of worthy causes.

Traveling continued to be a fascination. Dr. and Mrs. Ramsey in 1930 journeyed to Stockholm to attend the International Congress of Pediatrics and then went on to Oslo to the International Congress for Tuberculosis. The Russian government invited them to spend six weeks in the study of public health conditions. They also visited Finland and Poland. Upon his return to St. Paul, Dr. Ramsey reported on the use of tuberculosis vaccination in the Scandinavian countries, commented upon the possible harm that may come from the careless use of artificial sunlight, and described the systematic health examination given school children.

Retirement from practice only gave the Ramseys opportunity to have more time to devote to their interests and friends. Mrs. Ramsey, until her death in 1959, continued to write skilled verse and to be a warm and hospitable hostess. Both were always eager to support St. Paul's cultural activities. Dr. Ramsey, of course, continued his interest in the Children's Hospital. Indeed, he remained its medical director until he reached the age of 80. Even today, he remains a trustee and is successful in securing donations for the growth of the institution. When, in 1958, the hospital was greatly enlarged, the modernized old wing was named "Ramsey Wing" in honor of the *spiritus rector* of the institution.

Passing years seem not to have touched Dr. Ramsey much—he is remarkably active, and his interests have not flagged. It is hoped that his interest, displayed through the decades, will forever be an inspiration for the Children's Hospital and for pediatrics in this region, to which he has contributed so much.

PUBLICATIONS BY DR. RAMSEY

- WALTER R. RAMSEY: "History of the Children's Hospital, St. Paul, Minnesota." [1958]
- WALTER R. RAMSEY: "The Selkirk Colony on the Red River of the North: Its Profound Influence on Early Development of the Twin Cities." Privately printed [1952?].
- WALTER R. RAMSEY: *Infancy and Childhood: A popular book on the care of children.* E. P. Dutton & Co., New York, 1916, and J. M. Dents & Sons, London, 1916.
- WALTER R. RAMSEY: *Care and Feeding of Infants and Children: A Textbook for Trained Nurses.* J. B. Lippincott Company (Lippincott's Nursing Manuals) 1916. Philadelphia and London (2nd edition, 1920).

Book Reviews . . .

Otosclerosis

HAROLD F. SCHUKNECHT, M.D., *editor*, 1962. Boston: Little, Brown & Co. 660 pages. Illustrated. \$18.50.

Since about 1876 when Kessel, Miot, and others attempted to do stapes mobilization and stapedectomies through myringotomy incisions, otosclerosis has been a recognized clinical entity. The operations were considered to be worthless and exceedingly dangerous, however, and were abandoned by 1900. The disease did not appear on the horizon of modern medicine again until 1941, when Julius Lempert made popular the fenestration of the horizontal semicircular canal for restoration of hearing in the otosclerotic deaf patient. This new attack on the problem of otosclerotic deafness set off a chain reaction among otologists and researchers in the fields of otology, audiology, and the basic sciences. The resultant cloud from the original explosion has dispersed in all directions all over the world, and the resulting climate has been a healthy one. The controversial nature of the subject has stimulated wide diversity of opinion and much provocative thinking among the world's leading otologists and scientists.

In April of 1952, after eleven years of bypass surgery employing Lempert's fenestration procedure, Samuel Rosen reintroduced stapes mobilization through a new approach. This new mobilization procedure allowed far greater improvement in hearing, using a relatively safer and simpler operative technic than the fenestration. The procedure was modified and improved upon by many otologic surgeons until about the year 1957 when John Shea, Howard House, George Shambaugh, and others developed and popularized techniques for completely removing the stapes and replacing this ossicle with various types of prostheses. Today we find nearly as many restorative procedures for improvement of hearing in otosclerosis as there are otologic surgeons performing these operations. The one remaining fact concerning otosclerosis that all otologists and investigators agree upon is the obscurity of its etiology and pathogenesis.

Between the covers of this most informative book on otosclerosis, the reader will find clinical research and animal experimentation being pursued vigorously. The statistical information and published operative results are factual and precise. This book presents all of the basic science material pertinent to otosclerosis, vast amounts of statistical data from necropsy material and animal experimentation studies, realistic operative result analyses of the current microscopic surgical procedures employed in treating otosclerotic deafness, and the numerous diagnostic and therapeutic tools currently used by the otologic surgeons.

The book is a publication of the papers presented at the International Symposium on Otosclerosis sponsored by the Henry Ford Hospital of Detroit, Michigan, November 10 to 12, 1960. The contributors at this symposium numbered 44 plus an additional 10 discussers, all representing world-renowned practicing otologists and researchers in scientific fields directly related to otology. Almost without exception, each author's treatment of a particular subject relative to otosclerosis is well documented by beautifully illustrated pictures and graphs

of laboratory experimentation data and abundant clinical experience material with accurate illustrations of operative techniques. Also included are excellent histopathologic photomicrographs. Concise summary and conclusion paragraphs following each contribution provide for excellent rapid reading and review of each subject discussed at the symposium.

The book is highly recommended for the practicing otologist and otologic surgeon as well as for audiologists and basic scientists working in the field of otologic research and for fellows in otolaryngologic training. The book is not recommended for reading by the physician or student not completely oriented in the basic sciences pertaining to otologic research. Parts of the book, however, might be of considerable interest to geneticists, embryologists, anatomists, industrial physicians, and, most certainly, physicians who themselves may be afflicted with otosclerotic deafness.

GRAHAM G. SMITH, M.D.
Minneapolis

Drug Therapy

FRANK C. FERGUSON, JR., M.D., 1962. Philadelphia: Lea & Febiger. 411 pages. Paperback. \$7.50.

This is a useful but conventional reference text. In some 50 relatively short chapters it gives brief general discussions of the pharmacology of representative types of drugs, with consideration of choices and a short review of clinical use and then capsule accounts of representative individual drugs.

This volume is designed for quick reference purposes. There is no discussion of general principles of pharmacologic action or of the applications of pharmacologic knowledge to clinical use. Furthermore, there are no references, so that the reader has no help in finding further information on a specific drug in which he may be particularly interested.

The book is arranged conventionally and without much evidence of organizational plan. Unfortunately, this is characteristic of the stereotyped texts in pharmacology. Since this little book is devoted only to therapy, it omits consideration of many important drugs such as those used for diagnosis. Its consideration of drugs acting on the central nervous system is poorly organized; caffeine appears in the last chapter under "Unclassified Compounds" when there is already a section devoted to central nervous system stimulants.

The volume has a good index, and the information in it is clearly and succinctly offered.

CHAUNCEY D. LEAKE
Columbus, Ohio

Dissemination of Cancer: Prevention and Therapy

WARREN H. COLE, M.D., GERALD O. McDONALD, M.D., STUART S. ROBERTS, M.D., and HARRY W. SOUTHWICK, M.D., 1961. New York: Appleton-Century-Crofts, Inc. 462 pages. Illustrated. \$12.75.

It would be hard indeed to find a disease state about which so much and so little is known as cancer. We do not know the cause and cure, but a great deal of in-

(Continued on page 14A)



after surgery: vitamins are therapy

Nutritional supplementation is basic to postoperative care. Therapeutic allowances of B and C vitamins help meet increased metabolic requirements and compensate for stress depletion. STRESSCAPS can set the patient on a more favorable course and contribute to full recovery. Packaged in decorative "reminder" jars of 30 and 100.

Each capsule contains:

Vitamin B ₁ (Thiamine Mononitrate)	10 mg.
Vitamin B ₂ (Riboflavin)	10 mg.
Niacinamide	100 mg.
Vitamin C (Ascorbic Acid)	300 mg.
Vitamin B ₆ (Pyridoxine HCl)	2 mg.
Vitamin B ₁₂ Crystalline	4 mcgm.
Calcium Pantothenate	20 mg.

Recommended intake: Adults, 1 capsule daily, or as directed by physician, for the treatment of vitamin deficiencies.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.



STRESSCAPS®

Stress Formula Vitamins Lederle

BOOK REVIEWS

(Continued from page 326)

formation has accumulated within the last decade on the dissemination of cancer.

The authors of this volume have attacked this problem for several years. In this excellent, readable volume, with no padding, the authors have presented their researches in this field, both clinical and experimental. Lest the reader be misled, this book is of great practical value to the researcher, the clinician, and the student. The researcher has before him a clear, concise summary of the work done to date. The clinician has excellent, immediately applicable methods of treatment. The student has an "inspired account of the lives of cancer cells, starting with their detachment from the primary tumor, concentrating on the means of transportation by which they spread, and ending with the establishment by them of metastases."

Though written by surgeons who invariably are interested in the practical applicability of the findings of research, this book serves admirably as a source book of pure cancer research. References are up to date and pertinent. The information available is exactly what one would look for in trying to keep abreast of the field.

The general format of the book is excellent; discussions and concise summaries of many of the chapters serve to fix the information clearly. The over-all appearance of the book and the quality of illustrations are unusually good.

This book has little to detract from it. It is a must for those interested in the field of cancer and its therapy and treatment and should be on every practitioner's bookshelf.

IVAN D. BARONOFSKY, M.D.
San Diego, California

Medical Physiology

PHILIP BARD, PH.D., editor, *eleventh edition*, 1961.
St. Louis: C. V. Mosby Company. 1339 pages. \$16.50.

This edition of Bard's *Medical Physiology* retains the general plan of its immediate predecessor but also contains several important changes. The introduction of 5 new authors and the complete revision of sections on respiration, endocrinology, and neuromuscular systems are the most notable of these changes. In addition to these major revisions, a new chapter on physiology of muscular exercise has been included in this edition. In it there is an excellent discussion on the metabolic aspects of muscle exercise and the adjustments brought about in various organ systems as a result of exercise. The most interesting of the new sections is the one on neuromuscular systems, in which the biophysical aspects of nerve and muscle are described. This section, however, is also the one which is most likely to present difficulty to some of the readers for whom this book is intended.

A new format using double columns on each page makes this edition more readable than its immediate predecessor. There are numerous references given at the end of each chapter or section and conveniently separated into general references and original articles.

The stated purpose of this edition is "to present that part of physiology which is of special concern to the medical student, the practitioner of medicine and the medical scientists, in terms of experimental inquiries that have led to our present state of knowledge." Whether or not this edition amply fulfills this goal is a matter for speculation, but the fact remains that it is one of the better books presently available for this purpose. Its coverage is comprehensive and authoritative but, even

more important, it is extremely well written despite its many authors. All things considered, this edition is a better one than its predecessor and should be welcomed by the groups for whom it was intended.

GEORGE WERMERS, PH.D.
Minneapolis

Milieu Therapy in Schizophrenia

L.T. COL. KENNETH L. ARTISS, M.C., 1962. New York: Grune & Stratton Inc. 169 pages. \$6.00

In 1956 the author was one of the group who opened the experimental milieu therapy ward for the treatment of schizophrenic soldiers at Walter Reed Army Hospital. In this book Col. Artiss describes the establishment and operation of the ward and stresses the use of education in social behavior as a part of the treatment of the schizophrenic patient.

This small volume is divided into 5 sections. The first contains a description of the architectural and staff composition of the 10-bed unit. The author describes in some detail the "shakedown" phase and the initial period of staff distrust which must be overcome before such a ward can become an effective therapeutic tool. Even with abundant and experienced personnel, Col. Artiss discovered that, if the ward were to be maintained as a therapeutic instrument, he needed to spend 40 per cent of his time educating and working with the staff.

Experiences with group therapy and patient government are described in the second and third sections. The author traces the changes in his concept of the role of a group therapist as he continued to work with these schizophrenic patients. Only if he took the responsibility for maintaining group action would his schizophrenic group work effectively.

The fourth division contains the histories of 2 of the 27 successfully treated soldiers. The milieu seemed to provide the major therapeutic impetus for the first patient; in contrast, the second seemed to make gains primarily as a result of individual psychotherapy.

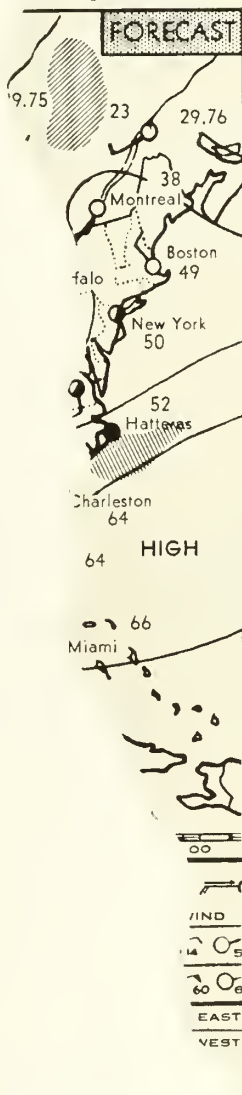
In the last section, the author discusses the theoretic foundation of the unit and speculates on the possible civilian applications of the study. The ward program was strongly influenced by Sullivan's idea that therapy with schizophrenics is education, "not by verbal teaching but by communal experience—good tutoring." The milieu described might be viewed as an attempt at social education.

One of the book's values lies in the many examples given of the environment's ability to shape behavior. In one instance a patient who shouted "Listen at me!" repeatedly while on the ward, stopped shouting the minute he passed through the door of the patient government meeting room. (The patients would not tolerate abnormal behavior in this room.) He participated in the business session, and only on return to the ward did he begin shouting again. Similarly, the unit's expectation that the soldier will recover and return to duty within six months (64 per cent of them did) must have had an important role in shaping the patients' eventual recovery.

The author sets forth his ideas on the therapeutic elements of the milieu; however, he fails to clarify what use was made of drugs or other somatic therapies. The two approaches—milieu therapy and somatic therapy—are not necessarily separate. Indeed, recent evidence suggests that a combination of the two may be superior to either method used singly.

(Continued on page 16A)

23, 1962



The Forecast

SUMMER COLD SPELL

Expected to dominate large areas of the country, with extended periods of swelling in the sinuses, upper respiratory infection and nasal congestion. Temperature ranges will be highly variable; patient's mood may be partly cloudy.

FOLLOWED BY CLEAR AND DRY

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1 a.m.	57	39	W 9	
2 a.m.	56			
3 a.m.	56			

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BOOK REVIEWS

(Continued from page 14A)

Besides being well written, this book provides a graphic account of the transformation of social psychiatric theory into everyday staff-staff and staff-patient interactions. In this sense it is down to earth and may offer practical parallels for those interested in the inpatient treatment of psychotics; however, for the psychiatrist who works with a large hospital population and for the investigator interested in theoretic concepts, the book has limited value.

KAY H. BLACKER, M.D.
San Francisco

The Church and the Older Person

ROBERT M. GRAY and DAVID O. MOBERG, 1962. *Grand Rapids, Michigan: Wm. B. Eerdmans Publishing Co.* 162 pages. \$3.50.

Empiricism and biased opinions have governed statements regarding the relationship of older people to the church and vice versa, the meaning of religion to older people, and the functions of the church in relation to older people until as recently as the last decade. More and more sociologic research is now being done in these areas, and studies thus far have involved several hundred people in large city churches, in rural areas, and in various types of institutions, both in the United States and Canada.

This book is a survey of knowledge obtained from these various studies in which the Burgess-Cavan-Havighurst Attitudes Inventory, which measures personal adjustment in old age, has played an important part. The work has been compiled by Robert M. Gray, assistant professor of sociology and preventive medicine at the University of Utah, Salt Lake City, and David O. Moberg, professor of sociology and chairman of the department of social sciences at Bethel College, St. Paul, Minnesota. In addition to reporting results of the surveys, there are an extensive bibliography and 2 valuable appendixes. Appendix I presents the "Basic Policy Statements and Recommendations of the Section of Religion" from the 1961 White House Conference on Aging. Appendix II makes "Suggestions for Further Study."

A definition of old age and a discussion of statistics regarding our aging population are concisely presented. Problems relating to physical, economic, social, emotional, mental, and spiritual areas, as well as the all important problems of the neglect of the aging, are also covered. The religious activities and beliefs of older people and their effects are presented with actual statistical studies in 3 chapters, followed by 4 chapters which summarize detailed data concerning various aspects of religious beliefs and activities and personal adjustments in old age.

The authors present a detailed discussion of what the church can do for older persons. The meeting of spiritual needs is but one important part of 10 specific areas covered. The last chapter sets forth 10 areas suggesting what older persons can do for the church. Education of older persons so that they might be better able to solve their personal problems and education of younger persons as to the preparation for aging are shown to be important, as is research.

It is apparent from the various studies that, while some churches are consciously studying and planning for the older members of their congregations, many are not. Many older people leave the church, not so much because they are physically or financially unable to attend

but because they feel they have been pushed out by younger members and are no longer wanted or needed.

It would seem (although further research is warranted) that church membership in itself does not contribute to personal adjustment in old age but that religious beliefs and activities possibly do. The findings also suggest that there is better personal adjustment to aging, as well as to death, if the individual has actively participated in religious activities in his younger years, rather than having turned to such activities late in life.

Concisely presented facts based on actual research as well as comprehensive references are presented in only 154 pages. The book is well written and easily read. This should be a valuable reference book, not only for ministers but for anyone who is concerned with the happiness and personal adjustments of the elderly individual. While many older persons may also gain understanding of their own problems from reading this factual report, it is certainly a book to be recommended for required reading in college classes in sociology or wherever problems of gerontology are being studied. Emphasis should also be given to the need for further research in this specific aspect of aging.

NILA KIRKPATRICK COVALT, M.D.
Winter Park, Florida

Uremia: Biochemistry, Pathogenesis and Treatment

GEORGE E. SCHREINER, M.D., and JOHN F. MAHER, M.D., 1961. *Springfield, Ill.: Charles C Thomas.* 487 pages. Illustrated. \$16.00

The authors' extensive personal experience with uremic patients is evident in this book. The uremic syndrome is precisely defined and differentiated from acute and chronic renal failure, specific renal insufficiency, and azotemia. Artificial dialysis is discussed, not only as a means of treating patients but also as an aid to the study of uremia. The section on biochemistry is composed of detailed analyses of the roles of the various anions, cations, and other substances contributing to the total electrolyte balance and osmolality of body fluids. The relationship of the multiple abnormalities in uremia to the various organ systems is well presented and includes thoughtful speculation and extensive documentation.

The treatment of uremia is bluntly stated to be beyond the grasp of the physician who has not given thoughtful consideration to the understanding of the complexities of the uremic syndrome. General principles of therapy are outlined.

This book is too detailed for general use but should be available for reference by the medical student, practicing physician, and the interested investigator. Several poor illustrations detract from the otherwise excellent format.

DONALD A. ROTH, M.D.
Milwaukee, Wisconsin

Clinical Hematology

MAXWELL M. WINTROBE, M.D., fifth edition, 1961. *Philadelphia: Lea & Febiger.* 1,186 pages. Illustrated. \$18.50.

Dr. Wintrobe's new book has been entirely revised so that all new advances in the last five years are written and discussed in detail. He introduces some of the biochemical steps involved in blood formation and the physiology of the hemopoietic system, together with many of the present concepts of erythrokinetics and leukokinetics.

(Continued on page 18A)

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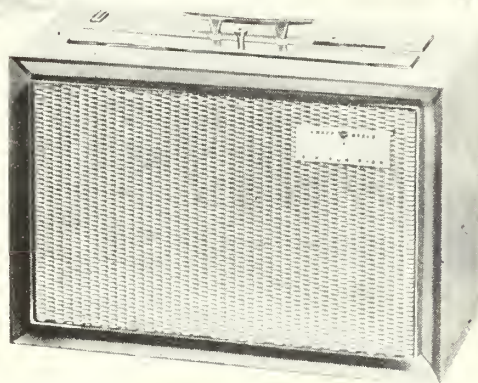
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BOOK REVIEWS

(Continued from page 16A)

He has brought the book up to date in the rapidly developing field of the hemoglobinopathies and also discusses many of the clinical manifestations.

The various bleeding disorders associated with platelets and coagulation of blood have been made simpler and more understandable. Many useful techniques in diagnosis, including radioisotopes, coagulation procedures, and other modern approaches, are described in detail. The book is more readable than his previous editions, and I feel it is easier to understand. He presents a wealth of knowledge; certainly anyone interested in internal medicine, hematology, or laboratory work would profit from a book of this type.

I think one of the most valuable contributions Dr. Wintrobe has given to hematology in this volume is the bibliography, which is so extensive that one may find references to the original articles. The 1,186 pages with 265 illustrations, of which 50 are in color, make this a complete and valuable book.

EDWARD N. NELSON, M.D.
Minneapolis

Textbook of Pathology: An Introduction to Medicine

WILLIAM BOYD, M.D., 1961. Philadelphia: Lea & Febiger. 1,370 pages. Illustrated. \$18.00.

This textbook is considerably enlarged and greatly revised in its present edition. One recognizes many old standard illustrations, such as a thrombus showing the lines of Zahn, but now there are many interesting figures illustrating pathologic processes by fluorescent techniques, as well as excellent electron micrographs of tumor cells.

Dr. Boyd has followed his previous philosophy of textbook writing—that is, to correlate pathology with clinical medicine. The organization is divided according to principles of pathology, such as the fundamental pathologic processes of inflammation, repair, coagulation, and so on. In these sections the author has included well-organized material on immunity and hypersensitivity, electrolyte imbalance, ionizing radiation, and nuclear genetics.

To characterize these areas, there is an excellent discussion of autoimmune disease, complete with illustrations including fluorescent microphotographs of glomeruli in lupus erythematosus, demonstrating gamma globulin deposits. Also included is a short discussion of tissue transplantation and its relationship to malignancy.

The second part covers pathology of organs and follows Dr. Boyd's previous path of correlating pathology with clinical findings. This portion will be particularly helpful to medical students for whom it is believed this textbook is particularly suited.

The chapters on specific organs, such as the kidney and lung, are greatly enlarged and thoroughly treated. Discussion of the adrenal gland is expanded, while the section on blood disease includes much more information on blood incompatibility, adrenal globulins, and hemolytic disease. A section on bleeding diseases is also included.

Chapters on bone and muscle are again expanded and include recently developed information. The last chapter on the teeth is more adequately handled than other textbooks on general pathology.

The book contains an extensive bibliography but does not include detailed information on less common pathologic processes.

OSCAR B. HUNTER, JR., M.D.
Washington, D. C.

Appendicitis in Infancy and Early Childhood

THOMAS K. BYRNE, JR., M.D., E. OMER BURGERT, JR., M.D.,
and HUGH B. LYNN, M.D.

Rochester, Minnesota

SINCE THERE APPEAR to be significant differences between appendicitis in infants and young children and that in older children and adults, we decided to make a study of appendicitis in the younger age groups only.

Among all cases of appendicitis in children 8 years of age and younger who were treated at the Mayo Clinic in the five-year period from January 1955 through December 1959, appendectomy was performed in 128. However, 61 of these cases were excluded from our definitive series because the appendectomy was done "incidentally" at the time of another intra-abdominal operation. It is of interest that in 2 of these excluded cases the primary cause of operation was Meckel's diverticulum containing bleeding gastric mucosa, the diagnosis of which had been accurately determined preoperatively.

This report, however, is concerned with the 67 patients in whom operation was undertaken because of suspected appendicitis. There were no deaths in this five-year series.

FINDINGS

Among the 67 cases, 56 (84 per cent) were acute at the time of operation. Rupture had occurred in 26 of these 56 (46 per cent) and abscesses had formed in 8 of the 26.

THOMAS K. BYRNE, JR., is a fellow in obstetrics and gynecology, Mayo Foundation. E. OMER BURGERT, JR., is with the Section of Pediatrics and HUGH B. LYNN is with the Section of Pediatric Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Incidence and ages. Our study confirms the statement by Longino and associates¹ that "appendicitis is rare during the first year of life, uncommon during the second year, but after that is seen with rapidly increasing frequency." We found no cases in the first and only one case in the second year of life, but thereafter the incidence increased. Perforation occurred in all patients less than 3 years old and in more than 50 per cent of those aged 3 through 6 (figure 1). All eight abscesses occurred in children 6 years of age and less.

Symptoms and signs. The often cited triad of abdominal pain, fever, and vomiting indicates appendicitis until proved otherwise. In very young children, however, this classic triad frequently is lacking. In our series, only 46 per cent manifested this symptom complex.

Abdominal pain was the most common symptom leading to operation for appendicitis. All of our patients complained of abdominal pain, although in one—a 4-year-old boy with a three-year history of recurrent episodes of abdominal pain, fever to 104° F., and vomiting—there were no acute symptoms at the time of operation. He was found to have a normal appendix with inflamed mesenteric lymph nodes.

Vomiting occurred one or more times preoperatively in 47 cases (70 per cent), of which 44 were acute. In 15 cases vomiting lasted longer than 12 hours; rupture was found in 13 of these.

Fever was considered present when the temperature was above 100° F. orally or 101° re-

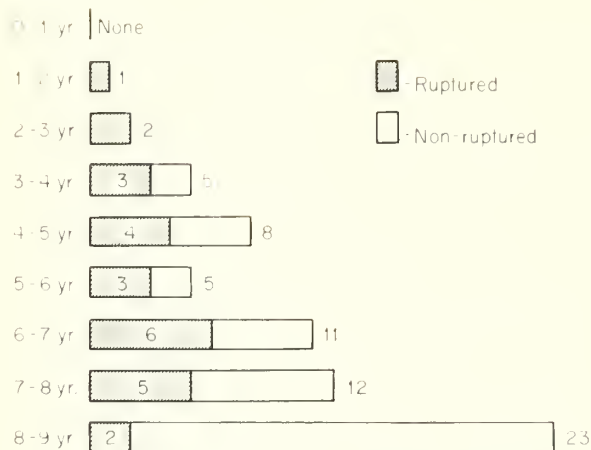


Fig. 1. Age at appendectomy, appendices ruptured and nonruptured

tally, as found in 42 cases (63 per cent). Among these, 37 patients had acute appendicitis and 5 had normal appendices. However, 16 patients with acute appendicitis had no elevation of temperature preoperatively.

Abdominal tenderness was elicited in almost all cases. Rectal tenderness was present in about 75 per cent.

Among the 8 patients with appendiceal abscess, a rectal mass was palpated in 6 but an abdominal mass in only 2, one of whom was in the rectal group also. Some authors² have considered rectal examination to be of no value in children, but we found it reliable in appendiceal abscess and advocate its use.

Peristalsis was recorded in only 46 cases. The abdomen was "silent" in 9 cases, among which the appendix was perforated in 7, acutely affected in 1, and normal in 1. Bowel sounds were notably present with 17 of the instances of perforation, although in many of these cases they were reduced from normal. Constipation was present in 11 cases and diarrhea in 6.

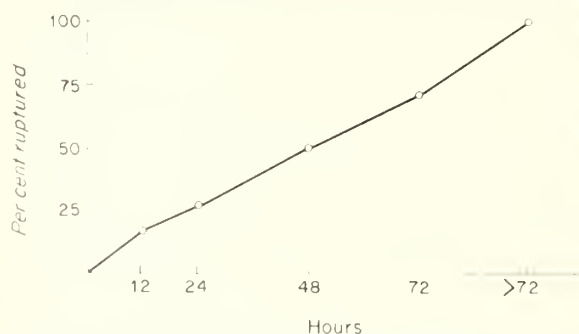


Fig. 2. Likelihood of perforation with increasing duration of symptoms. Note linear progression.

To determine whether perforation could be related to the duration of pain, we compared the cases of acute appendicitis (table 1). The linear progression found is illustrated in figure 2.

Laboratory findings. As seen in table 2, the leukocyte count was more than 10,000 per cubic millimeter of blood in 80 per cent of the 56 cases of acute appendicitis and in 36 per cent of the 11 in which the appendix was normal at operation. A left shift was found in 95 per cent of the acute cases and 45 per cent of the others. (The "left shift" in the differential leukocyte count is used here to denote that the polymorphonuclear cells and stab or band forms combined were more than 70 per cent.) Both an elevated leukocyte count and a left shift were found in 75 per cent of the cases of acute appendicitis but in only 9 per cent of the cases without appendicitis. In 5 cases the leukocyte count was above 20,000, which usually denotes perforation or the presence of some other disease. Of the 5 patients, 2 were studied by surgeons for two days and 1 for three days before a rectal mass was palpated. All of these 3 had perforated appendices with pelvic abscesses.

Thoracic roentgenograms, made preoperatively in 50 cases, gave evidence of pneumonia in 2 patients. One, an 8-year-old girl, had "resolving pneumonitis in the right middle lobe" which had not been detected on physical examination. Her appendicitis was acute. The other patient was a 4-year-old boy with pneumonia in the right lower lobe that was detectable by roentgenography and by physical examination. His appen-

TABLE 1
DURATION OF PAIN AND CONDITION OF APPENDIX

Duration of abdominal pain (hours)	Condition of appendix		
	Acute non-perforated	Ruptured Number	Per cent
0 to 11	7	1	13
12 to 23	10	3	23
24 to 47	10	9	47
48 to 71	3	5	63
72+	0	8	100
Total	30	26	

TABLE 2
RELATIONSHIP OF TOTAL AND DIFFERENTIAL LEUKOCYTE COUNT TO SEVERITY OF APPENDICEAL DISEASE

Condition of appendix	Cases	WBC >10,000	Left shift	Both*
Acute	56	45	53	42
Normal	11	4	5	1

*Both >10,000 WBC and left shift

TABLE 3
FECALITHS AND SEVERITY OF APPENDICITIS

Condition of appendix	Cases	Fecaliths	
		With	Without
Ruptured	26	16	10
Acute nonruptured	30	12	18
Abscessed	8	6	2

dix was retrocecal and acutely inflamed but not perforated. Before referral to the clinic he had been treated for four days with oxytetracycline (Terramycin) for the upper respiratory infection. These 2 cases demonstrate that acute appendicitis must be suspected even in the presence of unequivocal pneumonia.

Abdominal flat films were taken in 15 cases and revealed fecaliths in 3. One showed "opaque densities in the right upper quadrant—questionable artifact." At operation a perforated appendix containing a fecalith was found to be adherent to the under surface of the liver. Another patient was found to have a perforated appendix with a fecalith after the roentgenogram had shown "a calcific density over the right ileum—suspect fecalith." In the third case, roentgenography had to be repeated before the radiologist concluded that there was a "calcified mass in the right lower quadrant—a fecalith." At operation a perforated appendix with a 1.5-cm. fecalith was found associated with an abscess adherent to the right lobe of the liver and the gallbladder.

Pus cells (grade 2 or more) were found in the urine in 9 cases. The appendix lay along the right ureter in 2 of these; appendiceal abscess was present in 2 others. The finding of pus cells in the urine should alert one to the possibility of appendicitis, not rule it out in favor of other disease.

Operative findings. The condition of appendices in the series as a whole has been stated earlier. Fecaliths were found in 28 of the 56 cases of acute appendicitis, having been diagnosed roentgenographically in 3 as mentioned. Table 3 relates the incidence of fecaliths to the condition of the appendices.

Retrocecal or retroileal appendices were found in 10 patients (15 per cent). All 3 of the retroileal and 4 of the 7 retrocecal appendices were found at operation to be perforated. These cases point up the well-known fact that appendices located in abnormal positions tax even the most skillful diagnostician.

COMMENT

The difficulty of diagnosing appendicitis in infants and young children is well illustrated by the high incidence of rupture and abscess found at operation in the younger age groups.

A study of appendicitis in the Chicago area over the fifteen-year period from 1921 through 1935 revealed that perforation occurred in 40 per cent of cases involving young children: In 1959, Potts³ reported a study in the same area showing 41 per cent perforations. In our study, 46 per cent of the appendices had ruptured by the time of operation.

We wish to make a plea for early operation, with its attendant low mortality, rather than prolonged delay and vacillation with the likelihood of complications and inherent danger of perforation and abscess in this young age group. Because of the bizarre symptoms presented, the different responses to disease in young children, and the multiple childhood conditions which can simulate appendicitis even in cooperative small youngsters, we believe that in conscientious practice approximately 2 out of every 5 appendectomies should produce negative surgical findings. It is not the patients operated upon but those not operated upon who have the stormiest course. It is this neglected or "conservatively" treated group which shows the increased morbidity and later the complications and mortality—when surgery is finally undertaken.

SUMMARY

This study reviews the 67 operations done for suspected appendicitis in children 8 years of age and younger at the Mayo Clinic in the five-year period from 1955 through 1959. There was no mortality.

At operation, 84 per cent of the appendices were in the acute state, 46 per cent were perforated, and 12 per cent were abscessed.

The percentage of perforations gradually decreased with increasing age, reflecting the difficulty of diagnosis in younger children. The likelihood of rupture increased with the duration of symptoms, the presence of fecaliths, and anomalous location of the appendix.

A plea is made for early operative treatment of appendicitis in young children because its attendant morbidity and mortality are low in comparison with the danger of perforation and abscess formation when operation is delayed or withheld.

Read at the meeting of the Northwestern Pediatric Society, Bayport, Minnesota, September 22, 1961.

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Total Lung Capacity Among Healthy Chinese Adult Males

S. T. CHIANG, M.D., and JOHN Y. H. CHEN, M.D., F.C.C.P.

Taipei, Formosa

THE CLINICAL EVALUATION of the respiratory status in chronic diseases has been postulated by Baum and associates¹ to be: (1) the use of meaningful values which accurately portray the pathophysiologic changes and which can be determined easily, (2) the determination of normal values in healthy subjects with which the findings in disease may be compared, and (3) the use of serial measurements in the same position throughout the course of the disease.

Since the volume of air contained in the lung and the relation of its various subdivisions are affected by many disease processes, determination of total lung volume and its subdivisions may give useful information about the respiratory efficiency of the individual.² With the patient serving as his own control, serial measurements of total lung volume and its subdivisions in an individual patient can therefore be of considerable value in following the course of a disease process and in the evaluation of therapy.

Normal values of vital capacity and its subdivisions in Chinese have been published by many investigators.³⁻⁶ Functional residual capacity in adult Chinese males has been investigated by the method of Darling and reported recently.⁷ Total lung capacity in Chinese has been reported by Peng and Lin,⁸ with the functional residual capacity determined by Christie's method, which usually gives falsely large values.⁹ Up to the present time, there have been insufficient data among Chinese for comparative evaluation of the result. The purpose of this study is to establish the normal values of the total lung volume and its subdivisions, to analyze their intervolumetric relationships in normal subjects of a certain age, and to determine the effect of body size on total lung capacity.

MATERIALS AND METHODS

The 42 subjects investigated were healthy Chinese adults—physicians, medical and dental stu-

dents, and military officers—ranging in age from 21 to 34 years. Physical characteristics are shown in table 1.

The total lung capacity measurement required the determination of both functional residual and vital capacities. Vital capacity and its subdivisions—inspiratory and expiratory reserve volumes and tidal volume—were recorded on the Benedict-Roth metabolimeter. Functional residual capacity was determined by the open-circuit method of Darling.⁹ Residual volume was obtained by subtracting the expiratory reserve volume from the functional residual capacity. The total lung capacity was obtained by adding the inspiratory capacity to the functional residual capacity.

All measurements of lung volumes were made with the men in a sitting position and were corrected to BTPS (table 2). Both body height and weight were measured, the body surface area was obtained from Du Bois' body surface chart,¹⁰ and essential body mass was obtained from the chart prepared by Allen and associates.¹¹ All studies were done after a few minutes' rest in midmorning or midafternoon. The vital capacity and its subdivisions were determined first, and the subject was then switched to the instrument set up for the determination of functional residual capacity; 20 men were studied by the Douglas bag method⁷ and the rest were measured by the use of a Tissot gasometer, which was arranged as in figure 1. For the vital capacity and its subdivisions, at least 3 determinations were made. For the functional residual capacity, duplicate determinations were made for each individual and were checked to within 200 cc.

RESULTS

Results obtained from the study of 42 healthy adult men are shown in tables 1 through 4.

Lung volumes and capacities. The terminology of lung volumes and capacities recommended by a group of American physiologists in 1952¹² is used in this paper.

Mean values, standard deviations, (SD), coefficients of variation (CV), and standard er-

S. T. CHIANG and JOHN Y. H. CHEN are with the Pulmonary Function Laboratory, Department of Medicine, National Defense Medical Center, Taipei.

TABLE 1
AGE AND PHYSICAL CHARACTERISTICS OF 42 CHINESE MEN

	Age (years)	Height* (cm.)	Weight† (kg.)	Body surface area (m. ²)	Essential body mass (kg.)
Mean	26.31	169.55	57.28	1.66	48.74
Standard deviation	3.79	5.53	6.25	0.105	4.7
Coefficient of variation	14.41	3.26	10.91	6.34	9.64
Standard error	0.592	0.864	0.976	0.016	0.734

*1 cm. = 0.3937 in.

†1 kg. = 2.2046 lb.

TABLE 2
MEAN VALUES, STANDARD DEVIATIONS (SD), COEFFICIENTS OF VARIATION (CV), AND STANDARD ERRORS (SE) OF LUNG VOLUMES AND CAPACITIES IN 42 SITTING MEN (BTPS*)

	Inspiratory reserve volume (liters)	Tidal volume (liters)	Expiratory reserve volume (liters)	Residual volume (liters)	Total lung capacity (liters)	Vital capacity (liters)	Inspiratory capacity (liters)	Functional residual capacity (liters)
Mean	1.828	0.611	1.603	0.935	4.977	4.042	2.439	2.537
SD	0.296	0.14	0.277	0.257	0.724	0.552	0.358	0.319
CV	16.17	22.62	17.14	27.47	14.54	13.63	14.68	12.58
SE	0.046	0.022	0.043	0.040	0.13	0.086	0.056	0.05

*BTPS = body temperature, ambient pressure, and water saturation

rors (SE) of age and other physical characteristics of the 42 men are presented in table 1, and lung volumes and subdivisions for these subjects are presented in table 2. The mean vital capacity of 4.042 liters \pm SD 0.552 (table 2) is a little higher than those obtained by other investigators.³⁻⁶ The mean functional residual capacity in this study agrees with the value reported in a previous paper of the authors.⁷ The total lung capacity in this study is 4.977 liters \pm S.D. 0.724 (table 2). A somewhat higher value in the Chinese was reported by Peng and Lin,⁸ and much higher values were reported among occidentals by Western investigators.^{13,14}

Intervolume relationship. Intervolume ratios are shown in table 3. The vital capacity occupies 81.21 per cent of the total lung capacity. The inspiratory and the functional residual capacities fill up 49.03 and 50.97 per cent, respectively, of the total lung capacity. The ratio of residual volume to total lung capacity in this study is 18.79 per cent, which is very close to the normal value of occidentals. The inspiratory capacity constitutes 60.34 per cent of the vital capacity and the expiratory reserve volume, 39.66 per cent. They are of the ratio of 3:2 instead of 2:1, as was reported by the Western investigators.^{13,14}

Total lung capacity and its relation to body size. Table 4 shows the total lung capacity and its relation to body size in this study. The total lung capacity increases with increasing height, weight, body surface area, and essential body

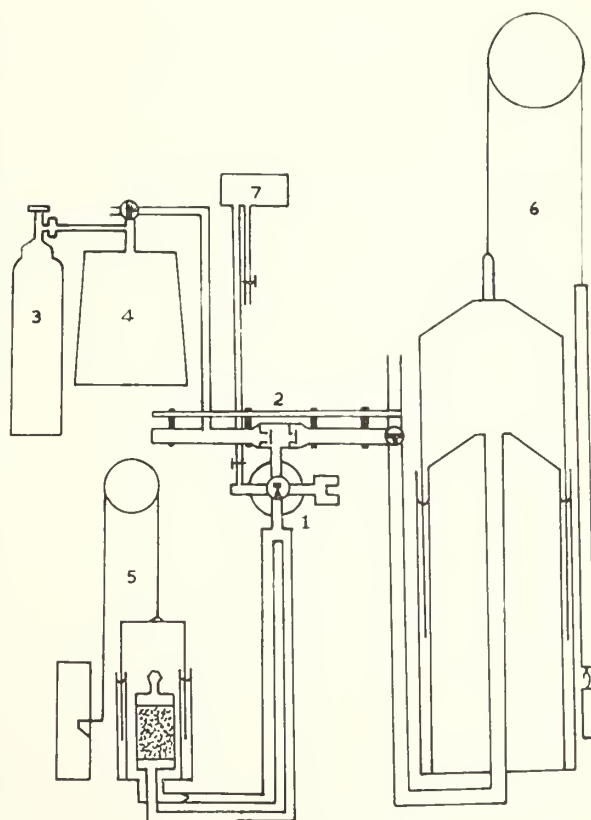


Fig. 1. Schematic diagram of apparatus. (1) Maurer 5-way valve. (2) Collins plastic 2-way "J" valve. (3) Oxygen tank. (4) Douglas bag. (5) Benedict-Roth metabolimeter. (6) 120-liter Tissot gasometer. (7) Sphygmomanometer rubber bag

TABLE 3
INTERVOLUME RELATIONSHIPS

	—This report—			—Birath ¹³ —			—40 sitting male subjects—			—40 lying male subjects—		
	Absolute value (liters, BTPS)	Per cent of TLC*	Per cent of VC†	Absolute value (liters, BTPS)	Per cent of TLC*	Per cent of VC†	Absolute value (liters, BTPS)	Per cent of TLC*	Per cent of VC†	Absolute value (liters, BTPS)	Per cent of TLC*	Per cent of VC†
TLC°	4.977	100.00	123.13	6.570	100.00	129.33	5.788	100.00	141.24	5.483	100.00	136.46
VC†	4.042	81.21	100.00	5.080	77.32	100.00	4.098	70.80	100.00	4.018	73.28	100.00
IC‡	2.439	49.03	60.34	3.390	51.60	66.73	2.708	46.79	66.08	3.027	55.21	75.33
ERV§	1.603	32.21	39.66	1.690	25.70	33.27	1.389	24.00	33.92	0.991	18.07	24.67
FRC	2.537	50.97	62.77	3.180	48.40	62.60	3.080	53.21	75.16	2.451	44.79	61.12
RV¶	0.935	18.79	23.13	1.490	22.70	29.33	1.691	29.21	41.26	1.465	26.72	36.46

°Total lung capacity

†Vital capacity

‡Inspiratory capacity

§Expiratory reserve volume

||Functional residual capacity

¶Residual volume

mass. In simple ratios, the data obtained in this study give a mean total lung capacity of 29.43 cc. per centimeter height, 87.24 cc. per kilogram weight, 2.959 l. or 2,959 cc. per square meter body surface area, and 106.58 cc. per kilogram essential body mass. Further analysis reveals that the total lung capacity is more closely related to the body surface area ($r = 0.502$) than to the height ($r = 0.403$), weight ($r = 0.424$), or essential body mass ($r = 0.427$). For practical purposes, a code number of 3.000 is used instead of 2.959, and the formula for predicting total lung capacity (in liters) can easily be derived by body surface area \times 3.000. According to this formula, all the values of total lung capacity in this study fall within a limit of -19 to $+15$ per cent. Using the method of least square, the equations of regression are derived whereby the relationships between total lung capacity and height, weight, body surface area, and essential body mass of these 42 men are well demonstrated.

The following formulas are the regression equations which can be used for predicting the total lung capacity from the height, weight, body surface area, or essential body mass of the subjects:

$$\text{If } X = \text{standing height, } Y = 0.0563X - 4.569$$

$$\text{If } X = \text{body weight, } Y = 0.049X + 2.170$$

$$\text{If } X = \text{body surface area, } Y = 3.414X - 0.6904$$

$$\text{If } X = \text{essential body mass, } Y = 0.0657X + 1.775$$

where Y = total lung capacity in liters and X = height in centimeters, weight in kilograms, body surface area in square meters, or essential body mass in kilograms.

DISCUSSION

The range of values from this study remains quite wide. The finding in this study reveals that the value of total lung capacity of the individual may deviate from the mean by as much as 20 per cent without apparent functional change of the lung. The total lung capacity correlates with the size of the individual, and the main determinant, as demonstrated in this study, is the body surface area.

Further analysis of the data (figure 2) indicates an even better correlation of total lung capacity with vital capacity than with body surface area. The r value of total lung capacity with vital capacity is 0.57, which is greater than the r value of total lung capacity with body surface area and other bodily measurements. Therefore, the use of vital capacity for predicting total lung capacity is even better than use of various physical measurements. Since vital capacity comprises about 80 per cent of total lung capacity,

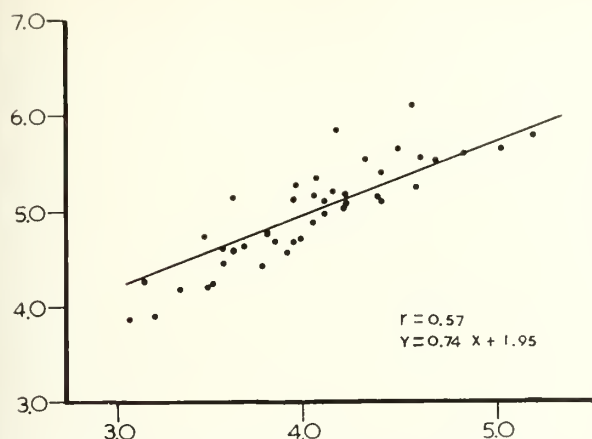


Fig. 2. Normal relationship of total lung capacity to vital capacity in 42 healthy Chinese adult males

it seems reasonable to use this for the prediction of total lung capacity.

The formula for predicting total lung capacity (TLC) from vital capacity (VC) has already been established. For the 21-35 age group, the formula is $TLC = VC/0.80$. Treating our data in the same way, the mean value of percentage difference from prediction is -1.45, and a range of -11 to +12 per cent is obtained. Since the formula of $TLC = VC/0.80$ is actually experimentally derived from the occidentals, our finding agrees with the concept that it can be used in spite of racial differences.

The ratios of functional residual capacity (FRC) to total lung capacity (TLC) and of residual volume (RV) to TLC have been found to be of great value in assessing pulmonary status. In this study, our value of the ratio $FRC : TLC$ is 50.97 per cent, which is not significantly different from those reported by Birath¹³ and Whitfield and associates.¹⁴ There are, proportionally, a slightly higher value of the expiratory reserve volume and a slightly lower value of the residual volume in this study, and

the ratio of $RV : TLC$ is a little lower than those reported by Birath and Whitfield.^{13,14} The vital capacity occupies 81.21 per cent of total lung capacity and is almost the same as the ratio predicted by Comroe.¹⁵ It is, however, slightly lower than that in the reports of Birath and Whitfield. In Birath and Whitfield's studies, the inspiratory capacity occupies about two-thirds and expiratory reserve volume one-third of the vital capacity; the present series shows that the inspiratory capacity is three-fifths and the expiratory reserve volume two-fifths of the vital capacity. The difference is statistically significant. Moreno and Lyons' study¹⁶ on the effect of body posture on lung volume indicated that, during postural change from supine to prone position, the inspiratory capacity decreased proportionately with increase of expiratory reserve volume. They explained this result as being due to the change of the level of diaphragm. Perhaps the daily habitual posture, especially the sitting habit, of Chinese makes the position of the diaphragm lower, which in turn affects the lung volume. Further studies may be indicated for proper explanation of this theory.

SUMMARY

1. Lung volumes and subdivisions of 42 healthy Chinese adult men have been determined in this study. The mean values were obtained, the intervolum relationships calculated, and the total lung capacity and its relation to physical characteristics analyzed.

2. Total lung capacity increases with increasing height, weight, body surface area, and essential body mass. The formulas, both in simple ratios and in regression equations, for predicting total lung capacity from height, weight, body surface area, and essential body mass were derived. Since, in this study, the best correlation was seen between total lung capacity and body surface area, the latter has been suggested to be

TABLE 4
TOTAL LUNG CAPACITY (42 SITTING MALE SUBJECTS)

	Mean \pm Standard error	Range
Age, years	26.3 \pm 0.592	21.00 - 34.00
Height, cm.	169.55 \pm 0.864	160.00 - 184.00
Weight, kg.	57.28 \pm 0.976	46.50 - 76.10
Body surface area, square meters	1.66 \pm 0.016	1.50 - 1.90
Essential body mass, kg.	48.74 \pm 0.734	38.00 - 58.00
Total lung capacity, l., BTPS	4.977 \pm 0.130	3.87 - 6.10
TLC, cc. per cm. height	29.43 \pm 0.896	23.70 - 36.60
TLC, cc. per kg. weight	87.24 \pm 0.903	70.00 - 110.00
TLC, l. per m. ² body surface area	2.959 \pm 0.704	2.43 - 3.28
TLC, cc. per kg. essential body mass	106.58 \pm 0.879	87.30 - 124

the parameter for predicting the total lung capacity from the physical measurements.

3. Relationship between total lung capacity and vital capacity is also analyzed. The correlation between these 2 variables is much better than that between total lung capacity and body surface area. Using the formula of $TLC = VC/0.80$, a mean value of percentage difference of -1.45 per cent from prediction, with the range of -11 to $+12$ per cent, was obtained in this study.

The authors wish to express their thanks to Miss H. Ho of the Pulmonary Function Laboratory, National Defense Medical Center, for her laboratory assistance.

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DIFFERENTIAL DIAGNOSIS in liver disease is facilitated by use of the auto-immune complement fixation test which helps to distinguish extrahepatic obstructive jaundice from parenchymal jaundice. Liver autoantibodies are found in the sera of (1) almost all patients with active primary biliary cirrhosis, postnecrotic cirrhosis, plasma cell hepatitis, lupoid hepatitis, or drug-induced jaundice; (2) some patients with lupus erythematosus; and (3) a few patients with acute infectious hepatitis. The autoantibodies are not found in the sera of patients with Laennec's cirrhosis, extrahepatic obstructive jaundice, or liver neoplasm.

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The Early History of Twin City Psychiatry

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AN INVESTIGATION of the development of psychiatry in the Twin Cities should note the prior appearance of this specialty in other areas of the state. This refers to the state hospitals which will merely be noted as a background from which to discuss psychiatry in the metropolitan area.

Even prior to the existence of any state hospitals in Minnesota, the State Legislature had authorized the governor, in 1863, to place up to 25 indigent insane in the Iowa State Hospital.¹ Later a few were also sent to Missouri. The first state hospital was conveniently built a fair distance from the populated areas, in keeping with notions of the time as to isolating the emotionally ill. This institution was placed 1 mile south of St. Peter. The first case was admitted to this State Hospital for the Insane on December 12, 1866.

A visit in 1872 by Doctors Hewitt and Daniels, acting as a committee from the State Board of Health, found that the institution could accommodate about 150 patients, but already 247 were confined.² The building was not completed but 2 sections and a basement were then being used. Dr. Cyrus K. Bartlett, the first superintendent, was brought from Northampton, Massachusetts, in 1868. In a book which he published in 1893, *A Brief History of the Minnesota Hospitals for the Insane*, he deplored the small amount of money spent for the care of mental patients; he advocated a tax of \$1.00 from every citizen in Minnesota, among other things, to remedy the situation.³ He had classified patients into 12 diagnoses, with the majority being "acute mania." There was no mention of treatment. When Hewitt visited the hospital again, in 1875, he noted that crowded conditions delayed admissions, and thus treatment, and that relatives only sent patients to the hospital when they became desperate in attempting to care for them at home.⁴ Much of this sounds very familiar to one work-

ing with the emotionally disturbed at the present time.

Minnesota's second hospital for the insane at Rochester, Minnesota, developed out of a conflict over the need for a Minnesota inebriate asylum. Work had begun on the building in 1876 but immediately a clamor arose to have it care for the insane instead of inebriates. Many groups, including Dr. Hewitt, believed it should be restricted to alcoholics, but in 1878 the legislature transferred all property of the inebriate asylum to a new institution for the insane which opened January 1, 1879. This was also supposed to care for the inebriates, but within two years its situation had deteriorated, with both groups kept together on single wards and the mentally disturbed being exploited sadistically by confined alcoholics.⁵ It is of interest that the medical staff of the Rochester hospital had even started publication of a quarterly psychiatric publication, "The Bulletin," in 1891, which lasted for 9 issues. It was discontinued because "the great majority of the profession have not as yet attained any great interest in mental disease."⁶ The superintendent of the hospital at that time was Dr. A. F. Kilbourne, who was appointed in 1889 and held the post until his death in 1934. He and his first assistant, Dr. Robert Phelps, were mainly responsible for this journal. Subsequent state hospitals for the mentally ill were established at Fergus Falls in 1890, when 80 patients were transferred from St. Peter; at Anoka and Hastings in 1900; and at Willmar in 1907, as a unit for inebriates which was later expanded to include all emotionally disturbed. In 1938 the newest state hospital was opened at Moose Lake.

By the time the first physician devoting himself to the specialty of neuropsychiatry began practicing in the Twin Cities, the first 2 state hospitals referred to were already filled with patients. The specialty had thus reached the state, though mainly in the form of physicians who worked in asylums and who had come here from other states. Many of the medical needs were met by local physicians practicing in the area who would visit the hospital as part of their charity work, such as Dr. William Worrall Mayo

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at Rochester. Records of the State Medical Society indicate only 5 neuropsychiatrists in the Twin Cities by 1900. These men will be discussed in more detail below: Doctors C. Eugene Riggs, Arthur Sweeney, Haldor Sneve, Charles Riggs Ball, and William A. Jones.

The first neuropsychiatrist in the Twin City area was Dr. Riggs (1856-1930) who arrived in St. Paul in 1881. He located here because of the widely prevalent opinion at the time that Minnesota climate, with its pine trees, might heal a pulmonary hemorrhage of suspected tuberculous origin. Much of this early history is contained in an address which Dr. Riggs gave in 1927.⁷ He stated that when he arrived in St. Paul the 3 outstanding neurologists in the country were William A. Hammond, S. Weir Mitchell, and Edward Sequin. At that time there were only 4 neurologists in New York, 2 in Boston and Philadelphia, and 1 in Chicago.

Dr. Riggs was an Ohioan and a graduate of the College of Physicians and Surgeons of Baltimore in 1880. This school later became part of the University of Maryland School of Medicine. A year after his arrival Dr. Riggs was appointed to teach a course on nervous and mental diseases at the St. Paul Medical College, which had just added this course to the curriculum and had no applicants for the position. To his fellow pioneer medical men of the state "nervous, and especially mental diseases, like x, indicated an unknown quantity in which they had little or no interest." When the College of Medicine and Surgery of the University of Minnesota was established as a teaching school of medicine in 1888, Dr. Riggs was made chairman of the Department of Nervous and Mental Diseases which he held gratuitously until 1913. The position was equal in rank and prerogatives with those of medicine, surgery, and obstetrics, but when it came to voting and faculty matters, the department vote was equally divided among the 3 major chairmen. The new department promptly included medical electricity and electro-physics as part of its curriculum on electrotherapy, a forerunner of what was to blossom out fifty years later as probably the most frequently used form of treatment administered to in-patients in this area, at least until the advent of the tranquilizers.

The medical students of that day were a "rough lot," Dr. Riggs quoted Dr. Beard to the effect that they were hard working, ambitious, and critical as ever, and passing a student over the amphitheater benches was a common pastime, as was concealing animals in reading desks or under seats, or introducing a corpse into a faculty meeting. He noted a feeling amounting

to an aversion on the part of students toward neurology and psychiatry which he believed due to lack of knowledge in the field at that time. To remedy the situation Riggs took postgraduate work in Edinburgh, with Dr. Alexander Bruce, and familiarized himself with the work of Golgi and Cajal. He brought back a microtome which Dr. Bruce had invented.

The first neuropathological laboratory in the state had been established by Dr. Riggs at the St. Paul Medical College, and the third case in the American literature of spinal cord changes from pernicious anemia was reported by him to the American Neurological Association in 1896. During the late nineteenth century the outstanding textbook was Hammond's *Diseases of the Nervous System*, which Riggs praised. However, he was critical of S. Weir Mitchell's "rest cure," believing it furnished "fertile soil" for the development of latent schizophrenic tendencies. As early as 1876, at a meeting of the American Neurological Association, Hammond had clashed with Dr. George M. Beard, of neurasthenia fame, over a paper on the influence of mind on disease and treatment. Hammond had commented that if he were to accept the doctrines of Beard, he "should feel like throwing his diploma away and joining the theologians."

Riggs had noted the decline in the 1920's of the types of hysterics seen in the Salpetriere by Charcot and wondered if it was associated with the increase in feminism coupled with larger opportunities, physical and mental. Besides the adequate testimony to his breadth of cultural and literary knowledge, from reading his papers I believe Dr. Riggs was progressive in many respects, although quite conservative in others. He did not hesitate to criticize the authorities when he felt they deserved it; he felt Kraepelinian nosology was passé at the time most of the profession were still eulogizing it. In May 1893, he made a plea before the North Dakota Medical Society for the voluntary commitment of the insane. Riggs pleaded for hospitals for the criminally and acutely insane as, "if an attack developed suddenly, without money or friends, these were placed in the common jail until commitment could be made—an act of barbarism." It must be noted that mental illness was viewed by the lay public, and by most physicians of the day, as a family disgrace which was accompanied by a great deal of shame, as it all too frequently is today.

On January 10, 1910, The Minnesota Neurological Society was organized. Its name was to be changed to the Minnesota Society of Neurology and Psychiatry in March 1932, for by that

time its membership included physicians whose sole interest was psychiatry. Dr. Riggs was elected president and other charter members were Drs. W. A. Jones, R. O. Beard, Leo Crofts, A. W. Dunning, J. B. Johnstone, Charles Riggs Ball, M. W. Jones, A. S. Hamilton, Arthur Sweeney, and Haldor Sneve. The Society was organized at the instigation of Dr. Riggs, who sent out invitations after Dr. Arthur S. Hamilton had already sent out his own a few days earlier. It was thus Hamilton's idea which Riggs appropriated, feeling he had to be the originator of the Society because of his senior position in the area at that time.⁸ This was apparently why Hamilton did not attend the first inaugural meeting. The first meeting was held at the Minnesota Club in St. Paul, and the second at the Minneapolis Club in Minneapolis, following which the meetings alternated between the 2 locations. The annual dues were \$5.00 the first year and thereafter were increased to \$7.50 annually. The first guest speaker was Dr. Archibald Church of Chicago, who spoke on "Family Tendency and Nervous and General Disease." He was subsequently made the first honorary member of the Society. The first person to be nominated for membership after the charter organization was Dr. F. H. Scott, a physiologist at the University of Minnesota; there is no record in the minutes that he was ever elected but he did begin to attend meetings the next year. The second individual nominated, on January 26, 1911, and elected to membership was Dr. Ernest M. Hammes, Sr., who is the senior neuropsychiatrist in the Twin City area at the time of this writing and who generously supplied material from his notes and records for this paper.

In 1911 the meeting place of the Society was changed to the Town and Country Club in St. Paul and regular meetings have been held there to the present time. Membership gradually increased, and by 1916 it was noted that the average attendance at meetings was 10 to 14 members, while initially it was 4 to 10. At that time an attempt was made to have the proceedings of the Society published in *The Journal of Nervous and Mental Diseases*, but it was unsuccessful. From May 20, 1918, to September 16, 1919, no meeting was held because of the war. At the first reunion 11 of the 19 members who had been in military service related their various experiences. The first meeting to be held outside of the Twin Cities was at Rochester, on June 4, 1930. Meetings have been held there since then and also in various other towns in the state.

Those who knew Dr. Riggs described him as having a reserved and dignified appearance and

an impressive personality, able to deal smoothly with other people. His manner was somewhat reserved and aristocratic. He was a deeply religious Congregationalist, dictating his own obituary six years before his death. His ancestors had come from an old, well-known Maryland family whose members played prominent parts in American history. He was a member of the Society of Colonial Wars and of the Sons of the Revolution, of which he had been a president.⁹ Riggs strenuously opposed the affiliation of the Mayo Clinic as part of the graduate medical program of the University. His feelings were so strong about a private institution's obtaining this special privilege that he resigned from the chairmanship of the Department of Nervous and Mental Diseases, along with several other members of the medical faculty, in 1913.¹⁰

It can be anticipated from this character structure that Dr. Riggs would have also been staunchly opposed to most of the teachings of Freudian psychology, and he was. He made reference to Freud's seizing the philosophical concept of the unconscious and evolving his own psychology from it. He noted that a writer of distinction had told him that literature had become so saturated with Freud that only 1 of 200 books reviewed by her was suitable for the home. He regarded Freudian teachings as a "sensualization of the social order" and felt that mental hygiene was frequently a masquerade for the exploitation of the Freudian idea, which lacks appreciation of "man's moral worth, of the sanctities of human nature, and of the divine impulses." This view is reminiscent of those traditional opponents of psychoanalysis who were mainly academicians and professors, imbued with what they considered "scientific psychiatry." Thus, Professor Weygand, in 1914, had held Freud's method was not a topic for scientific discussion but was a matter to be taken up by the police, and Professor Aseffenburg considered the theory wrong in most places, objectionable in some, and superfluous in all. Professor Oppenheim proposed a boycott of all institutions using the method, and Professor Spielmeier referred to the ease of Dorah as "mental masturbation."¹¹ These were the leaders in neurology and psychiatry during the period when Riggs pioneered in Minnesota and when he was forming his own concepts of mental functioning. Their influence, of course, did not "convert" him but became absorbed into his own predisposed views on human behavior.

A briefer look will be given at some of the other prominent men during the earliest period of neuropsychiatry in this area. Arthur S. Ham-

ilton was born in 1872 at Wyoming, Iowa. He received his Bachelor of Science degree from the University of Iowa in 1893, and in 1897 his Doctor of Medicine from the University of Pennsylvania. Following an internship in Philadelphia, he became assistant physician at Independence state hospital in Independence, Iowa, where he served with Adolph Meyer before coming to Minneapolis in 1904. He was destined to become the second chief of the Department of Nervous and Mental Diseases at Minnesota in 1913, following the resignation of Dr. Riggs. He remained as chief until 1935. Both of these men served gratuitously and maintained full time clinical practices while serving as chairman. The background of Dr. Hamilton varied widely from that of his predecessor. He had come from a poor country background in Iowa and had to finance his own education, with considerable hardship. He has been described as an affable, warm, and pleasing person, although reserved when in groups. His origins undoubtedly gave him a sympathetic attitude toward the struggling resident. It is recorded in the "Minutes of the Board of Regents" on December 7, 1927, that a gift of \$200 was accepted from Dr. Hamilton in part payment of the salary of a teaching fellow in the Department of Nervous and Mental Diseases.¹² During his tenure the Division of Neuropathology was instituted at the University. He was also one of the founders and past presidents of the Central Neuro-Psychiatric Association. One of Dr. Hamilton's main interests was medical history. He had given 3 addresses on the early history of medicine in Minneapolis before the Hennepin County Medical Society, in 1918, and at the time of his first cerebral vascular accident, in 1935, was preparing a history of medicine in Minnesota. The need for this can still be attested by anyone working in this field, as no such volume has yet been published.¹³

The second neuropsychiatrist who began practicing in the Twin Cities was Dr. William A. Jones (1859-1931). He had returned to Minnesota in 1881, the same year Dr. Riggs came to St. Paul, but went to St. Peter where he had been born and had attended grade and high school while working in his father's pharmacy. He was graduated from the University of the City of New York in 1881 and directly returned to Minnesota to become assistant physician at the state hospital for the insane at St. Peter. In 1883 he began general practice in Minneapolis but left in 1886 to study nervous and mental diseases at Berlin and Vienna before he returned to specialty practice. Like Riggs, he also came from "distinguished stock." Both maternal and

paternal grandfathers had served in the Revolutionary War and were of Scottish-Welsh ancestry. Although he was a prominent physician locally, he appeared to have a more cosmopolitan approach to medical affairs than his colleagues. Thus, not only had he been president of the Hennepin County and Minnesota State Medical Societies and of the Minnesota Academy of Medicine, but he was also a member of the American Psychiatric Association and the American Neurological Society, a charter member of the Minnesota Neurological Society and Central Neuropsychiatric Association, a chief of the Section of Nervous and Mental Disease of the American Medical Association in 1914, and vice-president of the American Medical Association in 1928-1929. He was active in arranging that the A.M.A. national convention be held in Minneapolis in 1928. He also served on the Minnesota State Board of Health from 1906 through 1918 and was president from 1911 on. His termination was due to the ever recurring theme of political machinations, as he was a supporter of Dr. Henry M. Bracken, who was secretary of the State Department of Health until 1919, when he resigned under pressure. This controversy involved Bracken with Governor J. A. A. Burnquist and Dr. Ignatious Murphy, Executive Secretary of the Minnesota Public Health Association who, Bracken felt, wished to abolish the State Board as it was then organized. Legislative disharmony was also prominent. The result was a failure of reappointment for Dr. Jones in the 1917 legislative session.

His academic career began in 1889 when he was made instructor in the Department of Nervous and Mental Diseases at the University of Minnesota, and from 1900 to 1919 he served as a full clinical professor. During his teaching career he was an "idol of the undergraduates" with a sharp wit and ready repartee. Those who remember him describe him as an excellent speaker who could turn the most routine of cases into an excellent teaching example. Dr. Hamilton described Jones as not a profound clinical investigator but one who could quickly grasp the outstanding features of a case and, though often of a snapshot variety, the diagnosis was usually correct.¹⁴ During the last years of his life he appears to have had a change in attitude. At that time he felt that teaching medical students was an unappreciative task for which one received no gratitude. He raised the question why physicians in practice should bother teaching ungrateful students. However, the vast majority of his life was spent as an able and stimulating instructor.

Most of his life had been hard work, with few vacations. His most enjoyable vacations were trips to New York where he would spend his days reading in his room on the top floor of a hotel, and his nights at the theater. He was an inveterate bibliophile, books being his main hobby. At the time of his death his library was left to the Hennepin County Medical Library. His other main hobby was music, and during his early career he supplemented his meager income by piano and organ playing.

His literary interests early led him to medical journalism. From 1901 to 1931 he was editor of *THE JOURNAL-LANCET* and contributed its editorials every two weeks for thirty years. This task was enjoyed immensely by him; the tone of his writing was provocative and challenging, and the editorials were dictated spontaneously, without notes. Many physicians stated they took the journal for "W.A.'s editorials." Until January 1, 1918, *THE JOURNAL-LANCET* had been the official organ of the Minnesota State Medical Association. In that year, *Minnesota Medicine* became the official journal after a heated controversy. One group urged Dr. Jones to consolidate with the new journal, which he would not consider. A series of blistering editorials appeared under his hand. For some time following, strained relations were apparent but in time the 2 journals settled down to maintain their parallel types of publications.

Another one of the early men in Twin City psychiatry was Dr. Haldor Sneve, who was born in Albert Lea, Minnesota, in 1865. He attended the public schools there until taking medical training at the College of Medicine, Ohio State University, from which he was graduated in 1887. Until 1890 he remained in Dayton, Ohio, advancing himself to assistant superintendent at the Dayton hospital for the insane. He was then offered a position as superintendent at the Rochester State Hospital in Minnesota, but turned it down to go into private practice in Minneapolis, with Dr. Dunsmore. In 1893 he went to Europe for two years, spending six months at Vienna and subsequently studying at Nancy, France. He then went to Stockholm and took a course in gymnastics and massage at the Royal Institute. It was probably due to the influence of his Vienna training that he became the "most ardent Freudian" in the area.¹⁶ In 1899 he moved to St. Paul from Minneapolis to become chief surgeon of the Chicago Great Western Railroad. Such a position seems anomalous to a physician sixty years later, but it portrays the nature of medical practice at the time. Specialization was then a very different thing.

No specialty boards existed and, as noted previously, the Minnesota Neurological Society was not founded until 1910. Sneve was a productive writer and published 20 articles, between 1895 and 1908, on topics as varied as myasthenia gravis, cystitis, mechanical treatment of constipation, reflexes, and general anesthesia. From 1896 to 1899 he gave a course of lectures at the University of Minnesota Medical School on mechanotherapy which were based on his Stockholm studies of gymnastics and hydrotherapy.¹⁷ In 1906 he sketched a bill for the establishment of a hospital farm for inebriates, which the legislature passed. From 1911 to 1914 he was a clinical professor in the Department of Nervous and Mental Diseases at the University of Minnesota Medical School, resigning because of negative feelings about the Mayo Clinic affiliation, as Riggs had done previously.

Although his acceptance of Freudian teaching contrasted him with his local colleagues, a similar picture of his personality is given. Thus, he was also the well-rounded scholar who frequently quoted great literature in his addresses. He was an ardent golfer and an enthusiastic violinist and met regularly with 3 other people for quartet playing. When illness was hampering his work in the last years of his life, he quoted Beethoven, saying, "I will grapple with fate; it will never pull me down." His addresses and presentations were described by Riggs as "thoughtful, interesting and entertaining." He was a man of strong opinions which were forcefully presented and argumentatively reasoned. He died in San Diego, California, in 1924.

Dr. Arthur S. Sweeney (1858-1928) was most prominent during his lifetime as an alienist, for which he had an international reputation. He was born in Lawrence, Massachusetts, and received his Bachelor of Arts degree at Fordham College and a Master of Arts degree at Georgetown University. He then attended Harvard Medical School and was graduated in 1886. He practiced in Lawrence for two years and then came to St. Paul. After six years of general medical practice, he returned to Harvard for postgraduate training in neurology and psychiatry and also studied in England and France before returning a specialist. From 1896 until his death he was a professor of Medical Jurisprudence at the University of Minnesota Medical School. He maintained an active interest in politics and was on the Legislative Committee of the State Medical Association for ten years. In 1902 he spoke feelingly of the weakening effects of politics in medicine, stating: "We have no real unity of efforts in prosecuting illegal practitioners so the

public views our efforts as petty prosecutions."¹⁸ In 1910 he had founded the South Side Sanitarium in Desnoyer Park for treating nervous diseases, in partnership with his close friends, Drs. Jones and Sneve. During the First World War he was chosen head of the Psychiatry Department at Camp Dodge, Iowa, where he devised tests for determining the intelligence of emigrants as well as one to be used on draftees. In the 1920's he was made a consultant by Congress in regard to the formulating of immigration laws and helped devise the statutes. Like Sneve, he was also employed by the railroads as a consulting neurologist to the Northern Pacific, Great Northern, Milwaukee, and Northwestern railroads. His effectiveness as an alienist was twofold; he was not only a recognized expert in the field, but his presence and sonorous voice were impressive. He had the admired qualities which most teachers desire, and few have, in presenting the most abstruse subjects in a clarifying and understanding manner. He was a co-founder, with Carl Ames, of the St. Paul Institute, which was dedicated to the education of people in artistic, literary, and historic events. It was supported by donations and financed many stimulating lectures. He was prominent socially and was active in the formation of the "Informal Club" which organized social activities in St. Paul. He died one week following a coronary occlusion.

Other early pioneers in the development of Minnesota neuropsychiatry will be mentioned briefly. Dr. Charles Riggs Ball was a nephew of Dr. Eugene Riggs. He initially shared an office with his uncle until 1918. During the summer it was the custom for Dr. Riggs to go on an annual vacation to the Blue Hills of Maine. During the summer of 1908 Dr. E. M. Hammes, Sr., recalled Dr. Ball's coming in to tell him that he did not plan to stay in the partnership any longer, and Dr. Hammes would have to handle the case load alone that summer. He later became associated with Dr. Hultkranz and Dr. Engberg, the current superintendent of the Fairbault State School. Dr. Ball was born in Bryan, Ohio, and was a graduate of Ohio Wesleyan College. He was graduated from the University of Minnesota Medical School in 1894 and subsequently took 2 graduate courses, at Harvard and Johns Hopkins, in nervous and mental diseases. He developed the first private laboratory in the Twin Cities where Wassermann tests could be performed on private patients. Dr. Ball died in San Diego in 1930, from a coronary occlusion. Unfortunately, no obituary appeared for Dr. Ball in *THE JOURNAL-LANCET OF Minnesota Medicine*.

The only one of the pioneers born in Minneapolis was Dr. Leo Melville Crafts (1863-1938), although some of his ancestors were among the founders of Boston. He was graduated from the University of Minnesota Law School in 1886 and then went on to study medicine at Minnesota, graduating in 1890. He interned at Boston City Hospital and served another year there as house physician. He then returned to Minneapolis to begin specialty practice in neuropsychiatry. Dr. Crafts had been appointed professor in the Department of Nervous and Mental Diseases in the medical department at Hamline University in 1893 and served in that position until 1908. He had also been dean of the medical department at that time, continuing until the absorption of the department into the University of Minnesota. He was described as a courteous gentleman who was a conservative, belonging to the Republican party, the American Legion, the Native Sons of Minnesota, and the Sons of the American Revolution.

Dr. Arthur Dunning died in 1915 at the age of 56. A charter member of the Minnesota Neurological Society, he was a graduate, in 1885, of the Physicians and Surgeons Medical College, Chicago. The last year of his life he suffered from angina pectoris. A few hours before his death from a coronary, a psychotic patient had attacked him, during which he struggled to get free. He was described by anyone who knew him or wrote about him as the most likeable of all the physicians of his day. His manner was one of kindness and considerate disposition. Riggs stated in his "Reminiscences" that "to know Dunning was to love him. He was gentle yet strong, sympathetic yet virile; in his heart there was the milk of human kindness—a gift indispensable if one is to reconstruct and reintegrate a crushed and hopeless personality." He devoted much effort to obtaining playgrounds for children in St. Paul, serving on the St. Paul City Playgrounds Committee for 3 terms. Dunning Field in that city is named after him as a memorial.

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ADMINISTRATION of antimalarial compounds suppresses systemic and discoid lupus erythematosus for a time, but relapses are common. Thus, long-term intermittent therapy is necessary. Only 4-aminoquinoline and related compounds are effective. Toxic reactions are numerous and severe. Of 67 patients treated with antimalarial drugs, 7 had complete remissions for three years or more without further therapy. Multiple relapses requiring repeated courses of medication were observed in 50 patients. The remaining 10 patients were benefited little or not at all.

R. K. WINKELMANN, C. F. MERWIN, and L. A. BRUNSTING: Antimalarial therapy of lupus erythematosus. *Ann. Int. Med.* 55:772-776, 1961.

CHILLING THE STOMACH WALL to between 10 and 15° C. will control massive upper gastrointestinal hemorrhage and may make surgical treatment of duodenal ulcer unnecessary. Bleeding from gastric tumors or because of blood dyscrasias is rarely completely stopped, however. Subsequent surgery is advisable for a patient with steroid ulcer, but the risk is diminished by hypothermia. The procedure should be considered when a bleeding patient fails to respond to sedation, transfusion, nasogastric suction, or milk drip.

D. M. NICOLOFF, W. O. GRIFFEN, JR., P. A. SALMON, E. T. PETER, and O. H. WANGENSTEEN: Local gastric hypothermia in the management of massive gastrointestinal hemorrhage. *Surg., Gynec. & Obst.* 114:495-503, 1962.

Office Diagnosis of Operable Congenital Heart Disease

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IT IS PRETTY WELL AGREED that some form of congenital heart disease is present in approximately 0.5 of 1 per cent of all births. It is also pretty well accepted that approximately 30 to 50 per cent of these children die within the first year. In the state of Washington, this would mean approximately 365 patients per year or 1 a day, to be distributed among at least 1,000 physicians interested in such problems. These physicians would include the general practitioner, the pediatrician, the obstetrician, and perhaps the internist. This is approximately 1 congenital heart patient per doctor every three years; approximately half of these are going to die within the first year, so this really means that each physician will treat 1 congenital heart patient every six years. Now, we're told we're going to have more doctors, but we're also told we're going to have more babies, so I would guess that this ratio would stay about the same. However, we're going to save some of these babies, so the number lost in the first year will probably decrease. Even then we are going to be faced with perhaps 1 congenital heart every three years.

From these figures alone, you can see the futility of going to the expense of installing extensive diagnostic equipment. One must learn to get along with those things that are available in most physicians' offices: the stethoscope, equipment for doing blood counts, and the roentgenographic and electrocardiographic equipment. In using this equipment one must also know its limitations. One must also realize that a cyanotic child should have a higher hematocrit than the normal child. In visible cyanosis there is 5 gm. of reduced hemoglobin in the circulation, so a cyanotic child with 8, 9, or 10 gm. of hemoglobin really is quite anemic, and he may be suffering from anemia rather than heart disease.

TYPES OF CONGENITAL HEART DISEASE

Although these figures seem to vary from clinic to clinic, one might say that in general the most

common defect is a ventricular septal defect. This is followed by patent ductus, tetralogy, atrial defects, pulmonary stenosis, tricuspid atresia, and finally, a left to right shunt with pulmonary hypertension. Another bit of information of historical significance is the fact that one, for the most part, finds a higher percentage of males with aortic stenosis, coarctation, transposition, and tetralogy, whereas there seems to be a higher percentage of females afflicted with patent ductus and atrial septal defects.

If the child is not in failure, if the heart is not greatly enlarged, and if growth and development are normal, there is probably no great hurry in sending him to a diagnostic center. It is my own personal feeling that we should know the exact nature of the defect before the child enters school but that there is no need of going to the more sophisticated studies unless the patient would benefit from complete repair of his defect.

DIAGNOSIS OF DEFECT

In the ordinary case of patent ductus arteriosus, there is a so-called to and fro murmur associated with a thrill, heard best in the subclavicular pulmonic area. This murmur is associated with a high pulse pressure of better than 40 mm. Hg, and sometimes on roentgenographic examination, one sees an increased blood flow to the lungs with a fullness of the pulmonary artery. Patent ductus arteriosus does not present a characteristic electrocardiogram other than perhaps a volume flow to the left side of the heart.

In coarctation of the aorta, the patient's femoral pulse should be checked regularly. Blood pressures should always be taken in both the upper and lower extremities when one is considering coarctation. The roentgenogram in coarctation is not characteristic in small children. Rib notching does not occur until later years. The electrocardiogram is not characteristic either. In fact, in the very small child we are more apt to find evidence of right-sided pathology than left-sided, as one would expect.

In tetralogy of Fallot, the child is moderately to severely cyanotic, depending entirely upon

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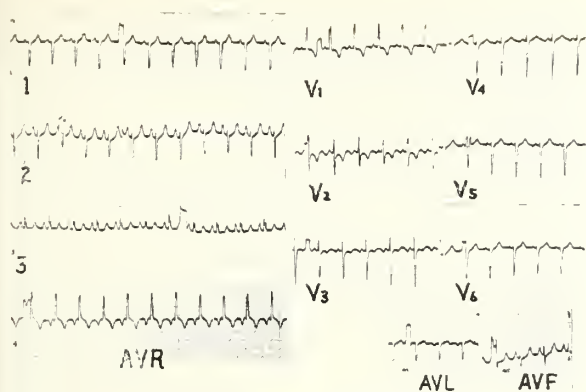


Fig. 1. Tetralogy of Fallot

the degree of blood flow to the lungs. Remember also that we do not have a large heart in this particular lesion, simply because of the nature of the defect. The right ventricle hypertrophies but does not dilate, so the over-all size remains essentially within normal limits. The roentgenogram, again, because of the blood flow to the lungs, always shows pale lung fields, and usually there is an indentation at the pulmonic area rather than the fullness that is present in most cases. The electrocardiogram in tetralogy always shows right-sided pathology with a positive axis in the standard leads, R waves over the right precordium, with RS to rs configuration over the left precordium. The P waves are usually peaked, particularly in lead 2 (figure 1).

In tricuspid atresia, the child is cyanotic, but his roentgenogram (figure 2) and electrocardiogram (figure 3) are characteristic. In the AP view, this child has a very flat border, and the heart appears larger than one would expect. In the left anterior oblique view, the left ventricle projects out over the body of the vertebrae, and the right border is very flat. The electrocardiogram shows evidence of left-sided pathology,

with a negative axis in the standard leads, with S waves over the right precordium and R waves over the left precordium.

In transposition of the great vessels, the child is cyanotic, but in this instance he almost invariably has a large heart with increased flow to the lungs. In the AP view the upper mediastinum is quite narrow, whereas in the lateral view it is wider than one would expect. The electrocardiogram, while not diagnostic, does give some lead in regard to the basic defects. At the present time these cases carry a rather high operative risk, and it is probably best that they undergo definitive diagnostic studies before one comes to any conclusion.

USE OF ELECTROCARDIOGRAM IN CHILDREN

I have spoken of right-sided and left-sided pathology, or peaked P waves, of the right and left precordium, and now I would like to tie this together. In the newborn infant, lead V₁ is usually an rSR'. V₆ is a QR complex, as are AVR and AVF, except that the Q in AVR may be a little larger. AVL is usually an rs. Taking V₁ as an example, remember that under one year of age, approximately 90 per cent of the cases will have an R that is greater than S. Between 1 and 2 years of age this drops to about 75 per cent. Between the ages of 3 and 5 this lead takes on the adult configuration, so that R is either equal to S or less than S in approximately 85 per cent of the cases; by the time the child is between 6 and 13 years of age, the proportion becomes approximately 90 per cent, or the same as one would find in adults. These findings are most important when one is interpreting electrocardiograms in children under 3 years of age.

In the last few years a good many of us have spoken of systolic and diastolic overload patterns in the electrocardiogram. For the most part, these fall into rather definite patterns, and

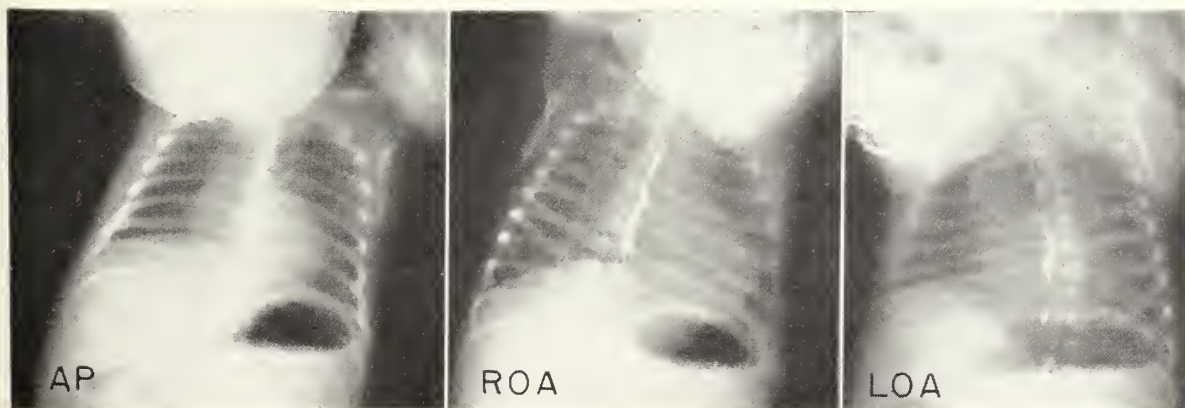


Fig. 2. Tricuspid atresia

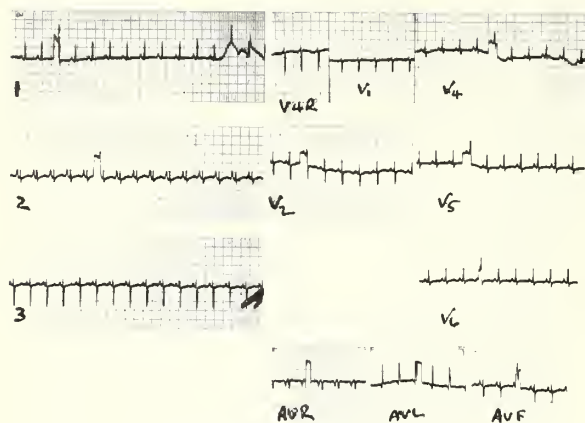


Fig. 3. Tricuspid atresia

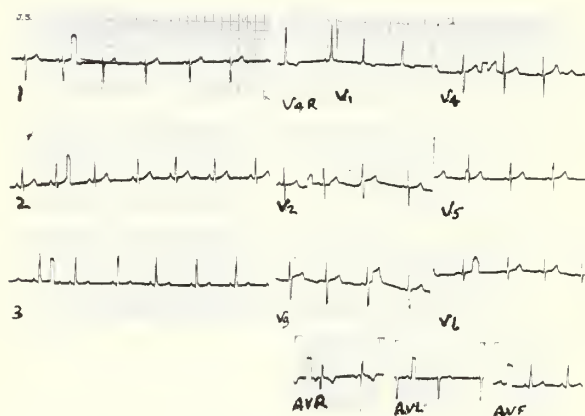


Fig. 4. Mild pulmonic stenosis—systolic overload of the right ventricle

I personally find these very helpful in diagnosing the type of lesion present. In a systolic overload pattern, there is increased resistance to the expulsion of blood during the systolic phase. As a result of this resistance, there is of course a delay in the onset of repolarization; consequently, the T waves of that area become flattened and negative. The potentials over this area are usually much greater, and various cardiologists have tried to correlate the height of the R wave in lead V_1 to the degree of resistance (pulmonic stenosis) present. In a systolic overload pattern of the right ventricle, one must remember that the pattern can be developed as a result of either a stenotic lesion, such as an infundibular or valvular stenosis, or it can be the result of pulmonary hypertension, so that one would see this pattern in isolated pulmonary hypertension, left to right shunts with pulmonary hypertension (atrial, ventricular, patent ductus), pulmonic, infundibular, or valvular stenosis, atresia of the pulmonary artery and, of course, in pulmonic

stenosis complicated by other lesions. The systolic overload pattern of the right side is usually characterized by a positive axis in the standard leads, a dominant S in lead I with a prominent R in lead 3. The R waves are dominant over the right precordium with usually a very small S wave (figure 4). For the most part the T wave

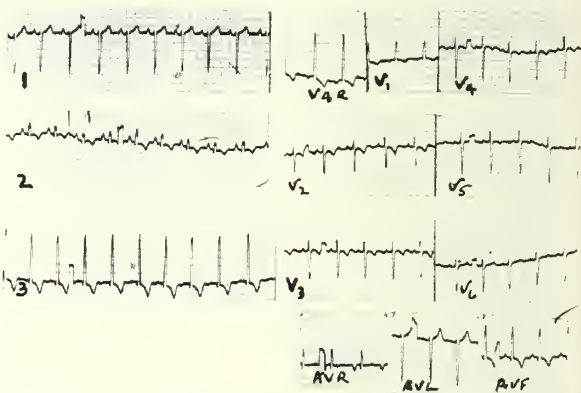


Fig. 5. Severe pulmonic stenosis—systolic overload of the right ventricle

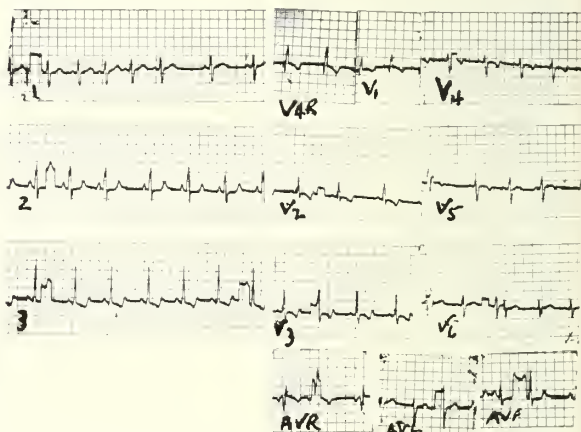


Fig. 6. Atrial septal defect—diastolic overload pattern

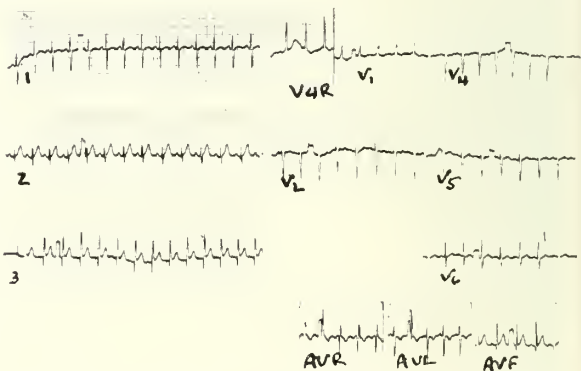


Fig. 7. Ventricular septal defect—combined right and left involvement with increased left ventricular work load

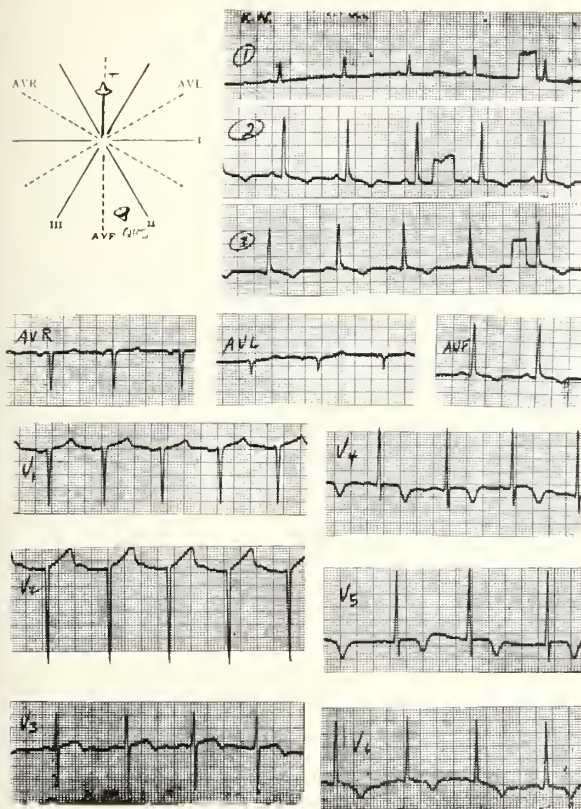


Fig. 8. Aortic stenosis—systolic overload of the left ventricle

remains upright, unless the resistance is high. Then the T wave is either isoelectric or negative and, if the pressure is extremely high, the entire ST segment is displaced downward (figure 5).

In the diastolic overload pattern of the right ventricle (figure 6), one usually finds evidences of right-sided pathology with a positive axis, but also there is an rR' over the right precordium. This volume overload pattern in many instances also results in an intrinsicoid delay. It is this rR' pattern plus the intrinsicoid delay and the normal ST segment that differentiates this type of lesion from the systolic overload.

The signs and symptoms of ventricular septal defects are of course dependent upon the size of the defect as well as the degree of resistance to the flow of blood to and/or through the lesser circulation. In general there is an increased work load on the left ventricle, resulting in enlargement and associated overload patterns. These patterns are best noted in leads over the

left precordium (V_5 and V_6) but should also be looked for in leads 2, 3, and AVF. Characteristically there is a Q wave of 3 to 4 mm. and R waves of 25 mm. or greater. T waves are large and peaked. In V_1 this increased left ventricular work load is manifest in an S wave of substantial depth (figure 7).

AORTIC STENOSIS IN CHILDREN

To my way of thinking, congenital aortic stenosis demands more consideration than all other congenital lesions combined. Children with aortic stenosis can and do die suddenly and violently. This is not necessary, providing one has adequate knowledge of the lesion and is respectful of the pathology. The early murmur of aortic stenosis is usually best heard in the pulmonic region, and then as the child grows older it progresses across the sternum and finally assumes its characteristic place in the aortic area. The murmur in question is nearly always associated with a thrill best felt in the suprasternal notch or over the right carotid. With this in mind I would then add the plea that whenever you hear a murmur in the upper mediastinal area, do not only feel for the femoral pulse but also hook a finger over the sternal notch and see if there is a thrill in this area. A few years ago we used to say that until one began to get ST segment changes in the electrocardiogram over the left precordium, one was reasonably safe in observing an aortic stenosis (figure 8). However, we have come to realize that this attitude is wrong, and that many children have severe aortic stenosis without electrocardiographic changes. I would, therefore, plead with you that if you consider a diagnosis of aortic stenosis, the child should be seen by a diagnostic laboratory and a left heart catheterization should be done to ascertain the difference between the pressures in the left ventricle and the aorta.

SUMMARY

Most congenital heart lesions can be diagnosed with the use of the stethoscope and electrocardiographic and roentgenographic equipment. These facilities are available to all physicians. Expensive and extensive studies are required in very few cases.

This paper was presented before the North Dakota Academy of General Practice, Williston, North Dakota, on November 17, 1961.

Danger of Depression Associated with Rauwolfia Therapy

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THE RAUWOLFIA DRUGS are used extensively in the treatment of hypertension. That depression is a potential danger accompanying such therapy, especially for patients of certain personality types, is indicated by reports in the literature and by our own experience. Vigilance by the physician also would appear to be advisable in this regard when products containing Rauwolfia are prescribed primarily for conditions other than hypertension.

Contained in the root of the Rauwolfia serpentina plant are many alkaloids.¹ Of these, reserpine was the first to be isolated and identified as an active ingredient. Rescinnamine, another alkaloid, and alkaloidal fractions such as alseroxylon, as well as preparations of the whole root, are now in use. Most recent additions to this drug group are an alkaloid isolated from Rauwolfia canescens (deserpidine) and a chemical modification of reserpine (syrosingopine).

Rauwolfia preparations or the pure alkaloids are marketed both alone and in combination with sedatives, diuretics, stimulants, and other agents. A partial list of trade name products containing some form of Rauwolfia is given in table 1.

REPORTS OF DEPRESSIVE REACTIONS

In studying the records of 202 hypertensive patients treated with Rauwolfia drugs for an average of ten months, Quetsch and associates² found that one-fourth developed depression. However, such reactions occurred in only 5 per cent of 185 hypertensive patients given no spe-

cific treatment. Among the Rauwolfia-treated patients with depression, onset of the complication was within the first six months of therapy in 60 per cent, within 6 to 12 months in 28 per cent, and after a year in 12 per cent. More than half the patients for whom previous depressive episodes had been recorded were affected. Of those without such a history, almost one-fourth developed depression; among these were the 8 patients most severely affected.

Ford³ reports depression in 6.9 per cent of 332 patients treated with alseroxylon and 61 per cent of 120 receiving reserpine. He also found that patients who had come to psychiatric attention before antihypertensive treatment were significantly more prone to develop adverse side reactions than other patients.

In a review by Achor⁴ of several published series, the following conclusions are suggested: Depression ensues in 15 to 25 per cent of hypertensive patients treated with Rauwolfia drugs, and 10 to 15 per cent of such reactions are moderate to severe. Although onset generally is within six months after therapy is begun, it can occur at any time; continual alertness on the part of the physician is therefore necessary. Depressive reactions are more frequent among older patients, with nearly equal occurrence in men and women. A history of mental illness, especially depressive reaction, is almost an absolute contraindication to administration of Rauwolfia compounds, especially on a long-term basis. Incidence of depression is unrelated to severity of hypertension, associated complicating disease, use of other drugs, or degree of blood pressure reduction induced by Rauwolfia therapy.

Dosage of Rauwolfia compounds, however, does appear to be a factor in occurrence of depression. Ford³ found a 45 per cent incidence

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TABLE 1
PARTIAL LIST OF RAUWOLFIA DRUGS*

From Rauwolfia serpentina		
Whole root Rauwolfia	Alone	Hyperloid Raudixin Rauserpa Rauval Rauwistan
	Combined	Hyperloid Mio-Pressin Rauproce Rautrax-N Rauverid Serbio Verwolfia
Purified alkaloids reserpine	Alone	Eskaserp Rauloydin Raurine Rau-Sed Reserpoid Sandril Serfin Serpasil Serpate Vio-Serpine
	Combined	Amril Butiserpine Diupres Du-Oria Estrosed Hydropes Meratran with reserpine Metamine with reserpine Penite Pentraline Protalba-R Reserpine with Mebaral Reser-Plus Resydess Ruhexatal with reserpine Rutaminal with reserpine Salutensin Sandril with Pylonil Ser-Ap-Es Serpasil-Esidrix Serpasil-Apresoline Serpatinin Solfo-Serpine Theobarb-R Tyandril Unitensin-R Veralba-R Vita Respital
rescinnamine	Alone	Moderil
Alkaloidal fractions alseroxyton	Alone	Rautensin Rauwiloid
	Combined	Pentoxylon Rauvera Rauwiloid + hexamethonium Rauwiloid + Veriloid Nitranitol R.S.
From Rauwolfia canescens		
Alkaloids deserpidine	Alone	Harmonyl
	Combined	Oreticyl
Chemical preparations		
Reserpine analog Syrosingopine	Alone	Singoserp
	Combined	Singoserp-Esidrix

*Drugs described in "Physicians' Desk Reference, 1961," ed. 15, Medical Economics, Inc., Oradell, N. J., 1960, and/or listed in "New and Nonofficial Drugs" (1961), J. B. Lippincott Company, Philadelphia, 1961.

of severe adverse reactions in patients taking more than 1 mg. of reserpine per day but only 20 per cent with lower amounts. Quetsch and associates² report an average daily reserpine dosage of 0.55 mg. for their patients who became depressed, whereas no depression was noted

with dosage of 0.2 mg. or less. "However," they comment, "it is possible that even this amount is not 'safe' under all circumstances."

Wilkins⁵ suggests that the dosage necessary to induce untoward effects, especially depression, decreases markedly with time in many patients.

TABLE 2
SUMMARY OF 8 CASES OF DEPRESSIVE REACTION ASSOCIATED WITH RAUWOLFIA THERAPY

Case no.	Age, (yr.)	Sex	Occupation	Blood pressure on admission	Type of depression	History of depression Patient	In family	Compulsive personality	Drug used	Duration of therapy before depression
1	67	F	Guardian	210/110	Neurotic	—	—	+	Rauwolfia	7 months
2	60	M	Executive	176/110	Psychotic	—	—	+	reserpine	10 months
3	42	M	Teacher	140/ 90	Psychotic	—	+	+	reserpine	2 months
4	44	F	Typesetter	170/110	Psychotic	+	—	+	reserpine	3 months
5	60	F	Domestic	152/ 92	Neurotic	+	—	—	reserpine	1 month
6	70	F	Housewife	184/110	Psychotic	—	—	+	reserpine	2 months
7	62	F	Unemployed	170/110	Neurotic	—	—	+	Rauwolfia	1 month
8	32	F	Bookkeeper	194/120	Neurotic	—	—	—	alseroxylon	2 weeks

According to Faucett,⁶ some patients, once recovered from drug-induced depression, develop early symptoms regularly and promptly if the compound is readministered. In hypertensive patients, use of Rauwolfia drugs seems to definitely enhance the likelihood of depression.

SUMMARY OF SELECTED CASES

We have found that people from different backgrounds and age groups, with divergent histories, can suffer from depression precipitated or at least complicated by the introduction of Rauwolfia drugs in their treatment programs. In 8 representative cases selected from our files (table 2), the patients' age range was from 32 to 70 years, with a median of 60. There were 6 women and 2 men with various occupations.

Of the group, 6 would be considered to have compulsive personalities. In order of frequency, the depressive symptoms among our patients were as follows: (1) anorexia; (2) insomnia, suicidal tendencies, despondency; (3) ineffectiveness, fatigue, agitation; (4) indecisiveness; (5) withdrawal from social contacts, forgetfulness, loss of sense of humor. It is important to note that, diagnostically, 4 of the patients had psychotic depressions.

Each of the patients had been given Rauwolfia in some form. As far as can be told from the records, the time between initiating drug therapy and onset of depression varied from two weeks to ten months. In all cases, treatment was by hospitalization and withdrawal of the Rauwolfia drug. In addition, antidepressants were given to 5 patients; electroshock was used for 1 patient not responding to antidepressants; and 2 patients were given electroshock without prior antidepressant therapy. In general, treatment is the same for depression associated with Rauwolfia therapy as for any other type.

REPORT OF CASES

Complications resulting from depression during antihypertensive therapy with Rauwolfia drugs

and potential problems in diagnosis and treatment of such reactions may be pointed up by 2 illustrative case histories.

Case 1. A 67-year-old unmarried woman was admitted to the University of Minnesota Hospitals on November 9, 1960, with symptoms of stomach pain, fatigue, depression, inability to do her housework, and a definite feeling of lack of sense of humor. She had been preoccupied with thoughts of suicide for two months before her admission.

Onset of fatigue, depression, and inertia apparently had occurred in 1956, after her sister had undergone an operation on her nose. With careful questioning, the following information was elicited. While the family physician was visiting the patient's sister to check on results of the operation, he took the patient's blood pressure. Because he found the pressure to be in the hypertensive range, he prescribed reserpine. The patient's symptoms began shortly after this. However, because of her rigid personality, the only complaint she mentioned to her physician for almost four years was "stomach trouble." Frequent roentgenographic and laboratory studies for signs of an ulcer, cholecystitis, or other organic disease failed to reveal any abnormalities. Only when the patient was admitted to the psychiatric ward was she able to acknowledge she had been severely depressed and suicidal.

Use of reserpine was discontinued, and therapy with a combination of tranlycypromine (Parnate) and trifluoperazine (Stelazine) was initiated. The patient was given the opportunity to talk about traumatic family experiences and received much support from ward personnel. On November 22, 1960, she was discharged from the hospital feeling, according to her statement, better than she had in six years. On outpatient observation ten months later, she was found to be maintaining her discharge status.

Case 3. A 42-year-old married man was admitted to University Hospitals on January 20, 1961. He complained of insomnia, anorexia, feelings of unworthiness, indecisiveness, and suicidal preoccupation. Onset was in December 1960.

The patient had recently been married after living for many years as a bachelor; someone who was very close to him had recently died; and, in addition, there had been staff changes associated with his job that were depressing to him. Of equal significance, however, was the fact that on previous routine physical examination he was found to have mild hypertension and was given reserpine. His symptoms began about one month after therapy was started. The patient's mother and father had both been hospitalized for depression.

Treatment included withdrawal of reserpine, administration of antidepressant drugs, and electroshock. He was discharged on February 10, 1961, feeling much improved. However, his condition did not remain stable, and further hospitalization has been required for the depression.

The outcome demonstrates our experience that depression associated with Rauwolfia therapy takes on the clinical aspects of any other type of depression and may be very difficult to treat successfully.

DISCUSSION

The factors which appear to be most important etiologically are the existence of a rigid, obsessive-compulsive, idealistic type of personality and a personal or family history of depression. We therefore recommend that physicians prescribing Rauwolfia drugs elicit from the patient information relative to the following questions:

1. Would you describe yourself as a perfectionist, worrier, or procrastinator?
2. Are you easily depressed?
3. Are you blue or depressed now?
4. Have you ever been treated by a physician for depression?
5. Has anyone in your family ever been treated for depression?
6. Has anyone in your family ever been given electroshock for any condition?

An affirmative answer to any of these questions would suggest the need for extreme caution in giving the drug, possibly reserving it for use only if the condition is uncontrolled by other medication.

Indeed, Perera⁷ questions whether, in terms of survival, drug therapy is superior to symptomatic treatment of primary hypertension. However, current practice leans sharply in the direction of using antihypertensive drugs. In this part of the medical armamentarium, Rauwolfia compounds remain basic.

To avoid adverse reactions, Ford³ recom-

mends that the dose of Rauwolfia used be the smallest one effective for the specific case. According to Achor,⁴ dosage in most cases probably should not exceed 0.25 mg. of reserpine, 200 mg. of whole root, or 4 mg. of alseroxylon. When Rauwolfia therapy is undertaken, Hoobler⁸ suggests that the patient and his family be warned of the possible insidious occurrence of depression at any time.

SUMMARY

Depression is a complication of Rauwolfia therapy occurring with sufficient frequency that the physician should be alert for this potential problem. Persons with rigid personalities, with obsessive-compulsive and idealistic tendencies, and with a personal or family history of depressive reaction seem to be most susceptible. Simple questioning of the patient regarding these factors will help to determine whether there is increased danger of depression ensuing. If use of Rauwolfia drugs cannot be avoided in depression-prone patients, the lowest effective dose should be given and close supervision maintained.

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Follow-up of Regularly and Irregularly Discharged Tuberculosis Patients

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DESPITE CHEMOTHERAPY, improved surgical techniques, mass roentgenographic surveys, tuberculin tests, and improved surveillance of tuberculous patients by public health departments, tuberculosis still poses a definite threat to the health of our nation.¹ One of the main factors that has undermined the hope for control and eradication of tuberculosis is the number of patients who continue to leave the tuberculosis hospitals before the completion of treatment.² They perpetuate their illness through their inability to overcome preexisting personal and social dysfunctions which increase their vulnerability to the disease and deplete their capacity to comply with a medical regime. Studies by Lorenz and associates,³ Calden and associates,^{4,5} Lewis and associates,⁶ Steininger and Howard,⁷ and Shelton and Sparer⁸ have been instrumental in identifying variables which lead to a favorable or unfavorable prognosis of the patient's ability to accept hospital treatment. The present study was undertaken as a continued exploration of factors which would differentiate the irregularly discharged patients from those who remain for the completion of hospital treatment.

SCOPE AND METHOD

Our report is based on a study conducted at the Veterans' Administration Hospital in Martinsburg, West Virginia, which consisted of a sample, comparative examination of 50 irregularly and 50 regularly discharged patients from July 1, 1958, to June 30, 1959. The initial universe included all patients removed from the Tuberculosis inpatient service during the study period. The universe was then dichotomized, a regular and an irregular discharge group being established.

For the purposes of research, the groupings

were more narrowly defined by exclusion of the following subgroups (Table 1):

1. All deaths
2. All patients who were not treated for tuberculosis
 - a. Patients who returned for tuberculosis check-ups only
 - b. Patients who received treatment not connected with tuberculosis, for example, bronchitis, pneumonia, emphysema, and surgery for non-tuberculous ailments
 - c. Patients who, during the course of observation, were maintained on antibiotics which they normally would have continued outside the hospital setting
3. All patients who received both regular and irregular discharges during the study period and those borderline discharges which could have been judged to be regular or irregular at the discretion of the staff physician.

The remaining population served as the study universe, from which the random sample of 100 cases, evenly divided between regular and irregular discharges, was drawn.

A schedule was constructed as the means for securing information pertaining to the variables expected to show differences between the groups. The variables were then explicated in the hypothetical statements of the study. Such statements were formulated on the basis of (1) professional literature which described the variables that purportedly distinguish the regularly discharged from the irregularly discharged tuberculous patient, (2) previous research studies which indicate discriminating factors between the two groups, and (3) impressionistic observations of colleagues and the author, who were involved in working with tuberculous patients.

According to the specified hypotheses, differences of findings between the regularly and irregularly discharged patients would be subjected to a test of critical ratio. This would determine whether the differences could be due to chance or could be considered statistically significant at a selected 5 per cent level.

The hypotheses tested in this study were that

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TABLE 1
PATIENT DISCHARGES FROM TUBERCULOSIS SERVICE
(July 1, 1958, to June 30, 1959)

	<i>Irregular</i>	<i>Regular</i>	<i>Total</i>
Number of patient discharges	77	552	629
Exclusions			
Deaths	0	29	29
TB check-ups	0	355	355
Non-TB	4	18	22
Observation	0	42	42
Irregular and regular	8	8	16
Borderline discharge	3	4	7
Total	15	456	471
Remainder	62	96	158

irregularly discharged patients as compared with regularly discharged patients are

1. More likely to have been employed in occupations which are considered to be lower in status
2. Less likely to have participated in occupational therapy while hospitalized
3. Less likely to have participated in educational therapy while hospitalized
4. Less likely to have participated in either occupational or educational therapy while hospitalized
5. Less likely to have participated in both occupational and educational therapy while hospitalized
6. More likely to have spent a longer cumulative period of time in VA hospitals
7. More likely to be problem alcoholics.

FINDINGS

Employment is considered as a measure of social status as well as of individual stability and achievement. Lorenz and associates⁹ discovered that the irregularly discharged patient "is less likely to have as skilled an occupational background as a patient who leaves with medical consent." The information compiled in this report complemented the findings of the Lorenz group. Using the social status rank order occupational categories of professional and business, white collar, skilled, semiskilled, and unskilled, it was determined that patients who are self-discharged without medical consent are more likely to have been employed in occupations which are considered to be lower in status ($P < 0.04$).

It was felt that the irregularly discharged patient would show his difficulty in adapting to the medical regime and therapeutic recommendations during the course of hospitalization. The

factors of emotional instability, lesser achievement, and social status usually associated with those most resistant to a professionally imposed discipline would be reflected by their unwillingness to participate in the opportunity for educational and/or occupational therapy. The self-destructive tendencies which are noted in patients who depart from the hospital without medical consent are seen in their forewarning rejection of occupational and/or educational therapy. This is borne out to a marked degree, as seen in table 2. For all categories, the irregularly discharged patients have not participated in therapy to the extent shown by the regular discharges ($P < 0.01$).

More specifically, the ratio of 3:1 participation in educational therapy and 2.7:1 participation in both occupational and educational therapy by the regularly discharged patients as compared to the patients receiving irregular discharges are also differences which are significant at less than the 0.01 level.

It was thought that the irregularly discharged patient would, as a result of receiving inadequate treatment, require successive hospitalizations for increasingly severe illnesses. (A study conducted by Shelton and Sparer at the VA Hospital in Memphis indicated that two-thirds of the repeaters had been self-discharges.)⁸ Successive hospitalizations would require lengthier stays in the hospital. This would mean that the irregularly discharged patient would, as an end product, spend a larger number of cumulative days in the hospital for treatment of tuberculosis. Previous studies^{3,8} have indicated that the irregularly discharged patients had less minimal disease and more far-advanced disease than the regularly discharged patients. This and other studies^{3,7,8}

TABLE 2
COMPARISON BY PERCENTAGE OF PARTICIPATION
IN SPECIFIED THERAPY BY PATIENTS RECEIVING
REGULAR OR IRREGULAR DISCHARGES

<i>Therapy</i>	<i>Participation of irregular discharges (%)</i>	<i>Participation of regular discharges (%)</i>	<i>Significant difference ($P=$)</i>
Occupational therapy	58	70	< 0.08
Educational therapy	10	30	< 0.01
Occupational or educational therapy	58	76	< 0.07
Occupational and educational therapy	19	52	< 0.01

have shown a high proportion of repeaters in the self-discharge group. Despite these findings, it did not follow that the irregularly discharged patient spent a longer number of days in cumulative VA hospitalization for treatment of tuberculosis. It was discovered that almost twice as many irregularly discharged as regularly discharged patients spent less than three hundred sixty cumulative days in hospitals; conversely, almost twice as many regularly discharged as irregularly discharged patients have spent more than three hundred sixty cumulative days in hospitals. The regular discharges averaged five hundred ninety-nine days of hospitalization, as compared to four hundred thirty-seven days for the self-dischargees. The hypothesis which stated that irregularly discharged patients are more likely to have spent a longer cumulative period of time in VA hospitals was rejected, and the antithetic hypothesis was accepted ($P < 0.05$).

In retrospect, results of the data can be attributed, at least in part, to several variables. For example, it appears reasonable to assume that mortality rates made heavier inroads on the self-discharge group due to the higher proportion of far-advanced disease among this group. Furthermore, many of the self-dischargees may have returned to private and state hospitals rather than to a VA installation. In addition, lacking the self-discipline and sense of social responsibility shown by the regular-discharge group, they may remain in the community as a threat to society and self. Factors other than the severity of the illness play the major role in determining their adherence to medical advice concerning hospitalization.

Anderson and others,¹⁰ in their study of non-hospitalized tuberculous patients, stated that "in only 6 per cent of the cases was alcoholism reported as a co-existing disease." Steininger and Howard,⁷ however, observed, in their study of 1,138 patients at the Maybury Sanatorium, Northville, Michigan, which they conducted in 1957, that 28 per cent of the original patients and about 50 per cent of the repeaters in their study were alcoholics. They consider alcoholism to be "a severe disciplinary problem, a serious impediment to cooperation, and a major factor in the frequent breaks in continuity of treatment among repeaters."⁷ The findings of this study, which compares the regular and irregular discharges, bear a striking parallel and approximation of the statistics presented by Steininger and Howard of the original and repeater groups. Of the group, 28 per cent receiving regular discharges and 58 per cent of the self-dischargees were reported as problem alcoholics ($P < 0.01$).

This aptly illustrates the dilemma of the staff physician in trying to decide where to place his emphasis on treatment. Although a major concern is the treatment of the patient's tuberculosis, the physician is aware that the problem alcoholic will often leave the hospital as soon as he regains his feeling of physical well-being, thus continuing the vicious cycle.

SUMMARY AND CONCLUSION

It is likely that the specific findings of this study, which indicate only a few of the many characteristics distinguishing the regularly discharged from the irregularly discharged patient, can be generalized, to wit: the irregularly discharged patients clearly presents accentuated intrapsychic and social instability in his everyday living patterns; is regarded as negligent, unsuccessful, and recalcitrant by the governing middle-class standards of our society; and is generally incapacitated for meeting the demands imposed upon him by the nature and extent of his tuberculous ailment. There is considerable evidence for the need of psychosocial therapy for the tuberculous patient as an inherent part of medical treatment. In many instances, the psychosocial needs of the individual are prerequisite to the need for antimicrobial treatment. It is necessary to fill sufficiently the unmet psychosocial needs in order to free the patient to the extent to which he can respond to the demands of the medical regime.

This study was conducted by Eugene Venables under the direction of Morris Kagan as part of the graduate school program of West Virginia University Department of Social Work.

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Observations on 101 Patients with Portal Hypertension

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ALTHOUGH CREATION of portal systemic shunts has become an established part of the surgical treatment of patients with portal hypertension, several authors have questioned the value of these procedures to prevent further hemorrhage, improve the patient's condition, or prolong life.¹⁻³ Because of this controversy, an evaluation of all patients with portal hypertension seen at the University of Minnesota Hospitals during the ten-year period ending December 1958 has been undertaken. From this study it appears that creation of such venous shunts reduces the incidence of recurrent bleeding from varices. However, since these procedures are attended by significant operative mortality and not infrequently are followed by hepatic insufficiency, these disadvantages must be weighed against their value in preventing death from hemorrhage.

CLINICAL MATERIAL

Because the ultimate prognosis of patients with portal hypertension depends in large part on the status of their liver function, patients have been classified for purposes of this study into 2 groups: those with intrahepatic block and usually impaired liver function and those with extrahepatic portal bed block and usually normal liver function. During the period studied, 83 patients with intrahepatic obstruction and 18 patients with extrahepatic portal vein obstruction were seen.

Portal hypertension due to intrahepatic portal vein obstruction

Patients were classified on the basis of the type of treatment they had received. Of the total patients with intrahepatic disease, 46 were managed nonoperatively, 31 were treated by the establishment of portal systemic shunts, and 6 were treated by other operations.

Patients treated nonoperatively. Several fac-

tors were considered in the evaluation. Esophageal varices were presumed to be present in all patients included in this study. In 33 of these 46 patients there was radiographic evidence of esophageal varices; postmortem examination confirmed their presence in 11 others. The clinical course was considered to be adequate to establish the diagnosis of bleeding esophageal varices in 2 patients. There were 29 males and 17 females ranging in age from 6 to 74 years; the mean was 49.7 years. The 6-year-old was a male child with fibrocystic disease and postnecrotic cirrhosis.

Severe hepatic impairment was demonstrated in these patients. All 46 had abnormal (greater than 5 per cent) retention of sulfobromophthalein, and 94 per cent had greater than 24 per cent retention. All but one of the group had serum bilirubin determinations in excess of 3 gm. per cent. Abnormal alkaline-phosphatase values (greater than 10 King-Armstrong units) and prothrombin determinations (less than 80 per cent) were recorded in 90 per cent of these patients. All patients in the group had reversal of the albumin-globulin ratio; 92 per cent had less than 3 gm. per cent of albumin.

The natural history of the disease is reflected in the clinical course of these patients and suggests that the nonoperative management utilized did not change the clinical course of the disease significantly.⁴ In this group, 33 patients had at least one episode of gastrointestinal hemorrhage. Often this was the event that first brought the patient to the physician, although one patient was known to have had varices for nine years before his first hemorrhage. Sixteen (56 per cent) died of their first hemorrhage or during the thirty days following the initial bleeding episode; 6 succumbed to recurrent hemorrhage and hepatic failure two months to seven years after the first hemorrhage, and 4 were lost to follow-up. With the exception of 1 patient who has survived for two years without recurrent bleeding, the remainder have died of other causes (table 1). Of the 13 who had no overt hemor-

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TABLE 1
FATE OF 46 PATIENTS WITH ESOPHAGEAL VARICES
GIVEN NONOPERATIVE TREATMENT

<i>Cause of death</i>	<i>No. of patients</i>
Hemorrhage	16
Hemorrhage and hepatic failure	6
Hepatic failure (6 months to 8 yrs.)	8
Hemoperitoneum following a gynecologic procedure	1
Monilial sepsis	1
Encephalitis and brain abscess	1
Coronary thrombosis	1
Leukemia	1
Carcinoma of liver (primary)	1
Lost to follow-up	5
Surviving	5
<i>Total</i>	46

rhage, 8 have died of hepatic failure, 4 are alive and well six months to four years following their initial hospitalization and 1 was lost to follow-up. Thus, for a patient treated nonoperatively, the risk of dying from variceal hemorrhage was 48 per cent within seven years of diagnosis of his disease, with 42 per cent dying within the first year from the date of diagnosis. An additional 17 per cent died of hepatic failure within four years of diagnosis.

Patients treated by portal systemic shunts. During the period of study, 31 patients underwent venous shunt procedures for the alleviation of portal hypertension due to intrahepatic disease. A total of 34 shunts was done, with 3 patients being reoperated upon because of recurrent variceal hemorrhage. There were 16 males and 15 females; the youngest patient was 15 and the oldest 65 years of age (table 2).

All patients treated surgically had esophageal varices and impaired liver function; 34 per cent had bled once and 15 per cent had bled more than three times before shunt operation. The varices were demonstrated preoperatively by roentgenographic study in 28 patients, by esophagoscopy in 2, and by splenoportogram in 1. With one exception, all patients had demonstrable abnormal liver functions with elevated alkaline phosphatase, serum bilirubin, and prothrombin time determinations by conventional standards.

The venous shunt procedures were of several types: Terminolateral splenorenal anastomoses in 15 patients, side-to-side splenorenal shunt in 1, end-to-side portacaval shunts in 17 patients, and a side-to-side portacaval shunt utilizing a vein graft in 1 patient. Three patients were operated upon a second time because of recur-

rent hemorrhage from varices; 2 of these patients had splenorenal shunts which had thrombosed and had portacaval shunts performed at reoperation. In the third patient, a splenorenal shunt was done because of thrombosis of the vein graft used to create his original portacaval shunt.

The results of these operations were considered both in terms of operative mortality and the subsequent course of the disease in the survivors. Of the 31 initial shunt procedures, 5 patients died in the postoperative period (within thirty days of operation) and 2 of the 3 patients operated upon a second time died within this period after their second operation, giving an immediate operative mortality of 22.6 per cent (table 3). One of these patients died from recurrent hemorrhage from varices. It was known at the time of operation that the splenorenal shunt had not lowered his portal venous pressure to a satisfactory level. There were 9 late deaths within three months to seven years following the operation. Of these patients, 3 died of recurrent hemorrhage and 3 of liver decompensation (table 4). The 3 remaining patients died of disease not related to portal hypertension. Two patients were lost to follow-up. Thirteen patients have survived six months to seven years (table 5); 6 of these patients have now survived more

TABLE 2
SHUNT OPERATIONS FOR PORTAL HYPERTENSION:
UNIVERSITY OF MINNESOTA HOSPITALS, 1948-1958

	<i>No. of patients</i>	<i>No. of shunt procedures</i>
Splenorenal shunt	15	17
Portacaval shunt	16	17
<i>Total</i>	31	34

TABLE 3
OPERATIVE MORTALITY

<i>Procedure</i>	<i>Cause of death</i>	<i>No. of patients</i>
Portacaval	Intraperitoneal hemorrhage	1
	Sepsis	1
Splenorenal	Peritonitis	1
	Upper gastrointestinal hemorrhage (13 days after operation)	1
	Sepsis, primary hepatoma	1
Portacaval followed by splenorenal	Intraperitoneal hemorrhage	1
Splenorenal followed by portacaval	Intra- and retroperitoneal hemorrhage	1
<i>Total</i>		7

than five years. Moderate to severe hepatic insufficiency is present in 4 patients and 5 have had recurrent variceal hemorrhage. None has developed peptic ulcer disease. Thus, of the 31 patients treated surgically, 9 (31 per cent) had recurrent bleeding and 4 (13 per cent) died of bleeding varices within two years after surgical treatment. Within three years of operation, 3 patients (10 per cent) died of hepatic insufficiency.

Patients treated by other operative approaches.

Portal hypertension and esophageal varices were treated by operations not primarily designed to lower portal bed venous pressure in 6 patients. These were done to stop otherwise uncontrollable variceal hemorrhage. Operations were successful in 4. However, 3 patients died in the postoperative period of sepsis, cardiac arrest, and aspiration pneumonitis; 1 bled again fifteen months later and died and 1 died of hepatic insufficiency three months after operation. The six patient survived, re-bled two years later, again had an esophageal vein ligation, and is alive two years after this second operation. It is readily apparent that this group cannot be compared with those patients who were offered portal decompression procedures.

Portal hypertension due to extrahepatic portal obstruction

During the period under study, 18 patients (10 males and 8 females) with extrahepatic portal obstruction were admitted to the University of Minnesota Hospitals. These patients ranged in age from 3 to 81 years. The disease was attributed to a number of etiologic factors. Thrombosis of the portal vein subsequent to neonatal omphalitis or intra-abdominal infection was as-

TABLE 4
LATE MORTALITY FOLLOWING DECOMPRESSION
OPERATIONS: INTRAHEPATIC PORTAL OBSTRUCTION

Procedure	Cause of death	Survival after operation
Portacaval shunt	Cancer of palate	3 yr.
	Hepatic insufficiency	10 mo.
	Hepatic insufficiency	18 mo.
	Hepatic insufficiency	4 ½ yr.
	Gastrointestinal hemorrhage	2 yr.
Splenorenal shunt	Coronary infarction	2 yr.
	Gastrointestinal hemorrhage	6 mo.
	Gastrointestinal hemorrhage	1 yr.
	Cancer of the cervix	1 yr., 4 mo.

TABLE 5
INTRAHEPATIC PORTAL OBSTRUCTION:
SURVIVAL AFTER SHUNT PROCEDURES

	Number	Per cent
Operative mortality	7	22.6
Late mortality	9	29.0
Lost to follow-up	2	6.4
Survivors	13	42.0
Total	31	100.0

sumed to be the cause in 5 patients and an additional patient had cavernous transformation of the portal vein without a clear-cut history of omphalitis. Four patients had splenic arteriovenous aneurysms. Leukemic hypersplenism was responsible for portal hypertension and esophageal varices in 1 patient. In the early period of this study the diagnosis of Banti's syndrome was made in 7 additional patients with esophageal varices and normal liver function as measured by conventional laboratory tests.

All patients in this group had esophageal varices. These were demonstrated graphically by esophagram in 13, by splenoportogram in 1, by esophagoscopy in 2, by laparotomy in 1, and post mortem in 1 patient. Varices had bled more than five times in 4 patients, 3 have had 4 bleeding episodes each, 3 bled three times each, 4 patients had one hemorrhage, and 4 patients never bled from their varices.

Patients treated nonoperatively. Only 2 patients in this group were treated nonoperatively for hemorrhage from esophageal varices. One was an 81-year-old woman whose varices occurred because of thrombosis of the portal vein following a pancreateoduodenectomy for carcinoma of the ampulla of Vater and postoperative subhepatic abscess. The other patient died at 34 years of age from congenital heart disease (hypoplastic left atrium and ventricle) and at autopsy multiple splenic arteriovenous aneurysms were found to be the basis of his portal hypertension. Both patients, therefore, died of causes not directly related to the esophageal varices.

Patients operated upon for extrahepatic portal obstruction. Many different operative approaches to this problem have been tried. Procedures designed primarily to lower the portal pressure in these patients are generally disappointing because it is difficult to maintain the patency of a shunt created between the small vessels usually encountered in children. In 2 patients the sole operative procedure was exploratory laparotomy; in 1, a 5-year-old boy, a shunt was not performed because of cavernous transformation of the por-

tal vein and the small size of the splenic vein. He has not bled since operation. The second patient had an operative splenoportogram which demonstrated a small portal vein but very large communications between the superior mesenteric and systemic veins. She has not bled in the two and one-half years since the operation, and her liver function studies are within normal levels.

One patient underwent end-to-side portacaval shunt after more than 5 episodes of bleeding from esophageal varices due to partial portal vein thrombosis. He rebled twice during the first month after operation and died one year later of recurrent hemorrhage.

Splenorenal shunts were created in 8 patients, 4 of whom are considered to have satisfactory results. These 4 patients are alive and well, without further hemorrhage two, seven, nine, and nine years, respectively, following their operations. One had bled three times before operation and 3 patients had each bled once from varices. Of the 4 patients whose shunts were failures, 1 bled twice, 1 three times, and 2 had 4 hemorrhages each before operation. One patient rebled three times since his shunt and has subsequently undergone esophagogastrectomy with jejunal interposition. This procedure failed, and the patient is awaiting reoperation. A second patient has been treated with transfusions for repeated hemorrhage following a splenorenal shunt performed at age 33 months at another hospital. The third patient had an esophagectomy for recurrent hemorrhage from varices one week after splenorenal shunt; he is awaiting further operation to connect the cervical esophagus to the stomach. Because of recurrent bleeding from varices, the last patient in this group had a subtotal gastrectomy six weeks after a splenorenal shunt. Three years later, again because of recurrent massive variceal hemorrhage, an esophagogastrectomy with jejunal interposition was performed. This patient is well, without subsequent hemorrhage, two years after the last procedure. Thus, of the patients in whom venous shunt operations are performed for extrahepatic portal obstruction, 50 per cent rebled and require extensive additional operations.

Operative procedures not primarily designed to lower the portal pressure were performed on 5 patients. One patient with cavernous transformation of the portal vein had a splenectomy followed in one year by a total gastrectomy because of recurrent hemorrhage from varices. At the time of the gastrectomy a liver biopsy was normal. She was treated by blood transfusions for repeated bleeding one, two, and three years later. Six years after the splenectomy, she first de-

veloped ascites which, although of small amount, persists thirteen years after the first operation. She has not had hemorrhage from varices for eight years. A second patient underwent near total gastrectomy one year after splenectomy because of 2 bleeding episodes following the original operation. He is alive eight years after the second procedure and has had one episode of variceal hemorrhage five years ago. A third patient had a splenectomy followed ten years later by total gastrectomy because of recurrent hemorrhage. He has survived thirteen years since the latter operation, having had one bleeding episode nine years ago. Another patient is alive and well, without hemorrhage, four years after an esophagectomy with jejunal interposition. The last patient in this group underwent several operations over a fourteen-year period because of recurrent bleeding from esophageal varices due to cavernous transformation of the portal vein. She is alive and well without recurrent hemorrhage three years after her last procedure (esophagectomy with loop esophagojejunostomy). It is evident that splenectomy alone or with limited esophagogastric resection usually fails to prevent recurrent hemorrhage. The fact that there was no operative mortality suggests that these patients with normal liver function are better operative risks than the patient with intrahepatic disease.

Thus, of the 9 patients who had venous shunt procedures for extrahepatic portal hypertension, 5 (55 per cent) rebled and 1 (11 per cent) died of recurrent hemorrhage. All 4 patients with splenectomy alone rebled and required additional operative procedures; they have all rebled after esophagogastrectomy following the original splenectomy.

DISCUSSION

Valid conclusions regarding the efficacy of portal systemic shunt procedures for relief of symptoms and ultimate improvement of the patient's prognosis cannot be drawn from so small an experience as these figures suggest. However, it is to be noted that these statistics are not unlike those reported elsewhere and in much larger series.^{1,3-8} Portacaval shunts undoubtedly do reduce the likelihood of recurrent hemorrhage, although, as noted by others,^{4,9} we have seen repeated and severe hemorrhage after such a procedure. Blakemore¹⁰ reports an incidence of 19 per cent recurrent bleeding, although he readily concedes that in many of these patients, the anastomosis has become occluded.

Evaluation of the influence of venous shunt procedures on the prognosis is accurate only if

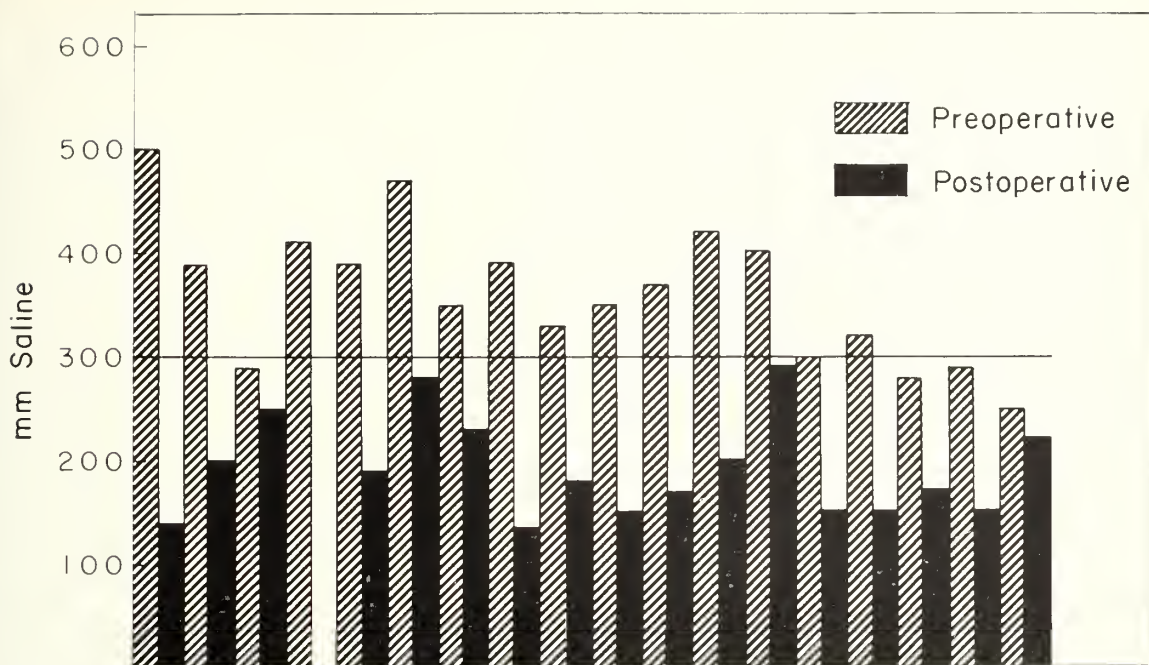


Fig. 1. Pre- and postoperative portal pressure as recorded in patients undergoing portacaval shunt procedures at the University of Minnesota Hospitals, 1948-1958

one has a comparable control group. Several authors^{1,11} have alluded to the difficulties in making such a comparison between patients treated surgically and those upon whom no operation was performed because of certain methods of selection of patients subjected to operation.

These methods usually eliminate some 40 to 60 per cent^{4,8} who succumb to their first hemorrhage, exclude a large number of patients with poor liver function,¹² and include a number of patients who have survived a substantial period of time after their first hemorrhage before opera-

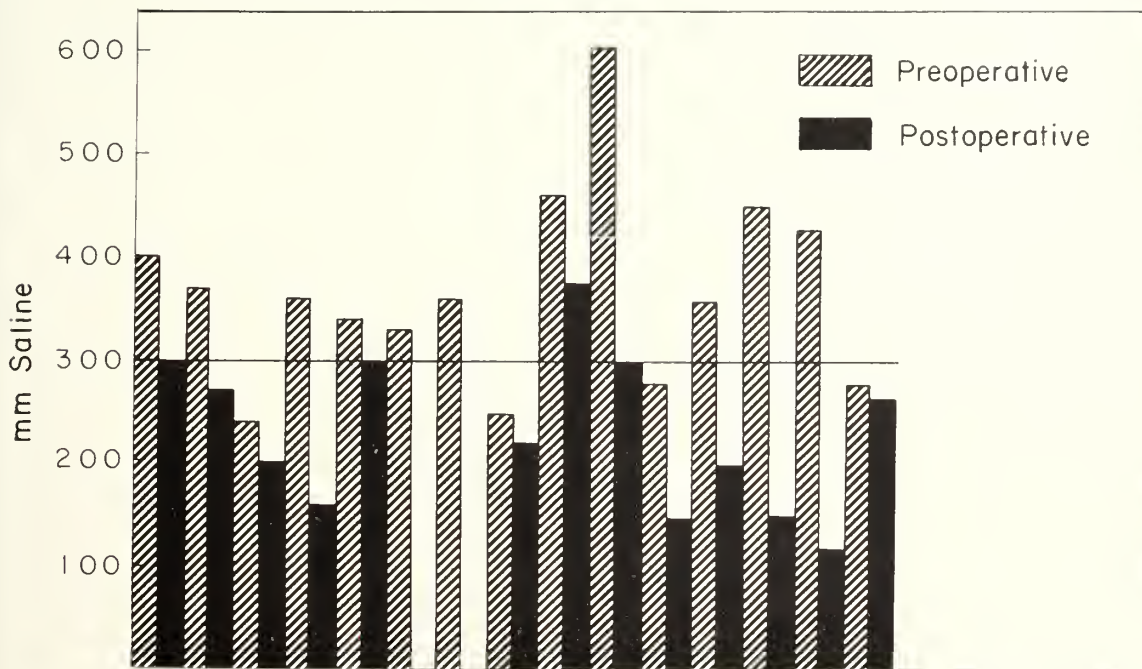


Fig. 2. Pre- and postoperative portal pressure as recorded in patients undergoing splenorenal shunt procedures at the University of Minnesota Hospitals, 1948-1958

tion. Ratnoff and Patek⁴ and Palmer⁷ have shown that the death rate for the first year after hemorrhage is very high and tends to fall off thereafter. Thus, all those operated upon more than one year after their hemorrhage have managed to survive without decompression and they are not altogether comparable with the remainder of the surgical group.³ Only 4 patients with intrahepatic obstruction in this series were operated upon more than one year from the date of their initial hemorrhage, and an additional 4 had never experienced frank upper gastrointestinal bleeding.

Portal decompression procedures are attended by a significant operative mortality in the group with intrahepatic obstruction (22.6 per cent). Following these operations some patients who had demonstrable lowering of their portal pressure to 300 mm. saline or less^{11,13} (figures 1 and 2) did rebleed. Recurrent hemorrhage in the group with extrahepatic portal obstruction is eliminated in 50 per cent of the patients by decompression operation and markedly reduced only by resorting to near total esophagectomy.

Although there were patients with varices and

presumably portal hypertension who did not bleed, the failure of nonoperative management contributes to a grim situation. Patients with bleeding varices who do not respond to nonoperative treatment of massive hemorrhage uniformly die within the first few days of hospitalization. Thus, there exists justification for emergency decompression surgery in an attempt to improve what otherwise would be a 100 per cent mortality rate.

SUMMARY

A review is presented of all patients with portal hypertension seen in the University of Minnesota Hospitals in the decade ending December 1958. In the group with intrahepatic portal vein obstruction, 31 had venous shunt operations, 6 were treated by other operative approaches, and 46 were managed nonoperatively. Of the group with extrahepatic obstruction, 9 had venous shunt procedures, 7 were treated by other operative approaches, and 2 were managed without operation. Shunt operations have been found to reduce the likelihood of recurrent hemorrhage but are noted to be accompanied by significant mortality and morbidity.

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Measles (Rubeola): A Clinical Review

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SINCE CURRENT TEXTBOOKS provide excellent source material on the subject of measles,¹⁻³ no attempt will be made here to include a comprehensive description of the disease. Rather, considerations with reference to clinical practice will be emphasized to provide a background for review of effective methods for managing the patient with measles and its complications. A brief summary of some recent reports concerning experimental observations relative to the status of measles vaccine will be included in this review.

Measles is a widely prevalent, sometimes fatal, communicable viral disease, usually occurring in childhood. After an incubation period of ten to twelve days, the virus will attack the mucous membranes and submucosa of the conjunctivae and upper respiratory tract. This manifests as a prodrome consisting of conjunctivitis, coryza, and increasingly severe cough, accompanied by an enanthem in the oropharynx and subsequently followed by the occurrence of superimposed discrete lesions on the buccal mucosa, traditionally called Koplik spots. After the four- to six-day prodromal period, a morbilliform or maculopapular rash occurs which erupts first about the neck and face and progresses to the trunk and extremities. The latter stage is often accompanied by hyperpyrexia, exhausting cough, and prostration.

The earliest pathologic lesion of measles probably begins late in the incubation period and is fully developed in the prodromal period. It consists of accumulations of multinucleated giant cells in the reticuloendothelial and lymphoid tissues, including that of the tonsils and the appendix. Involvement of the latter may give rise to acute appendicitis late in the incubation period or during the prodrome. The mechanism for the formation of the giant cells is not definitely

known, but they are considered to be specific for measles. They disappear soon after the rash develops.

Subsequently there occurs a perivascular round-cell infiltration and congestion in the mucous membranes of the eye and upper respiratory tract, which causes the characteristic inflammation and mucopurulent exudation in these tissues. This pathologic process also involves the blood vessels, hair follicles, sweat glands, and deeper layers of the skin and clinically gives rise to a variable amount of periorbital edema and puffiness of the face. Koplik spots also represent areas of perivascular infiltrate in the submucous glands, and the white flecks consist of foci of epithelial cells undergoing necrosis and fatty infiltration. The inflammatory process is followed by general desquamation of the mucous membranes and skin.

The changes in the lung are characterized by congestion of capillaries and a mononuclear interstitial bronchial infiltration, resulting in a thickening of the walls of the bronchi and bronchioles. These areas of thickening, together with accompanying purulent exudate, may present as multiple miliary-like areas of consolidation on roentgenograms. The mediastinal lymph nodes are often considerably enlarged, even when pneumonia is absent, and may persist into convalescence. Although these pulmonary lesions are initiated by the virus, they produce conditions in the mucosa of the respiratory tract favorable for invasion by pyogenic organisms. Secondary bacterial infection is most often caused by the streptococcus and pneumococcus, but occasionally the staphylococcus and influenza bacilli can also give rise to a patchy or confluent pneumonia.

Another pathologic process in the lung, known as giant-cell pneumonia, can occur. The lesions are characterized by the formation of multinucleated giant cells which differ from those that initially develop in the lymphoid tissue. These giant cells in the lung contain nuclear and cyto-

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plasmic inclusion bodies which arise from the respiratory epithelium of the lower respiratory tract in association with an interstitial pneumonitis.⁴ Giant-cell pneumonia is a distinct morphologic entity which may and often does develop without a rash or other signs of measles. On the basis of new diagnostic technics, it has been demonstrated that Hecht's giant-cell pneumonia is identical with and probably represents a measles giant-cell pneumonia without the rash. Giant-cell pneumonia may follow the subsidence of the clinical evidence of measles, the virus being found at autopsy. This might indicate that in some instances the measles virus may persist and be the cause of severe and sustained illness after the initial infection, even as long as up to thirty-five days after the rash.

Since giant-cell pneumonia is usually fatal, it has, therefore, been suggested that the disease develops as the consequence of an immunologic breakdown on the part of the patient. Viral multiplication in lymphoid tissue results in rapid production of antibodies. In giant-cell pneumonia it is thought that antibodies do not develop because of inadequate function of lymphoid tissue.⁵ Recently reported cases have occurred most frequently in children being treated for acute leukemia or having other debilitating disease.⁶

The nature and the extent of the neurologic disturbances associated with measles has not been clarified. In a study of 717 patients with measles, Gibbs and associates⁷ reported that 37 patients had clinical evidence of encephalitis and that all 37 had abnormal electroencephalograms. Of the remainder without clinical evidence of encephalitis, 51 per cent had electroencephalographic abnormalities in the acute and postacute period. The significance of this remains to be evaluated by further observations.

The histologic features in measles encephalitis are like those found in other types of post-infectious encephalitis which may develop with mumps, chickenpox, influenza, and following smallpox vaccination. The outstanding change consists of extensive perivascular demyelination of the brain and cord. Since there is usually a latent period between the onset of the disease and the encephalitis, it has been suggested, but not proved, that this represents an autoimmune response to damaged brain tissue.

The symptoms of measles vary in duration, severity, and time relationship, possibly depending somewhat on the age of the patient. The younger the individual, the more likely the clinical course will be typical. The incubation period is ten days, with outside limits of seven to four-

teen. The prodromal period, which usually lasts four days, is ushered in with fever and malaise. Within about twelve to twenty-four hours the patient may develop some puffiness of the lids, congestion of the conjunctivae, and beginning cough.

The oropharynx and tonsils become suffused the second day of the prodromal period. This enanthem consists of lesions which are quite discrete and appear as multiple, scattered, pin-head-sized brown spots. As the congestion becomes more marked, the spots become more numerous and confluent and there may develop superimposed miliary vesicles. The enanthem fades as the temperature returns to normal. A severe enanthem may cause considerable pain.

Between the second and third day of the prodromal period, when the respiratory signs and symptoms become more severe, the Koplik spots, which comprise the first pathognomonic evidence of measles, will appear. They have been likened to grains of white pepper on a red background, as apt a description as any. They first appear on the buccal mucous membrane opposite the first molars and then spread to the rest of the mouth. Koplik spots may sometimes be noted on the mucous membranes of the gums, inside of the lips, lacrimal caruncle, nose, and vagina. They appear rapidly as discrete lesions but are quickly obscured within about twelve to eighteen hours by the more general inflammation of the skin and mucosa.

A nonspecific transient rash may occur in the first day or two of the prodromal period which should not be confused with the exanthem. The lesions may be macular, scarlatiniform, or urticarial. They disappear before the onset of the typical exanthem. This type of prodromal eruption may also occur with the onset of other respiratory and communicable diseases.

About two weeks after exposure and about thirty-six hours after the first appearance of the Koplik spots, the exanthem will occur. The patient at this time will usually be acutely ill. The rash develops first on the face and neck behind the ears and progresses down the trunk and extremities over a period of four to five days. It fades in the same order of appearance. Some years ago, however, the diagnosis of an acute illness in a young college student was initially puzzling to his attending physician—as well as to me when I saw him in consultation—because along with his respiratory symptoms a morbilliform eruption developed, first on the lower extremities. The rash subsequently spread to the trunk and finally to his face, at which time he presented the full-blown picture of measles.

The earliest lesions develop as small, faint, red macules and soon become papular and irregularly confluent. In severe cases, the rash is most confluent and may be accompanied by marked hyperpigmentation and development of petechiae and ecchymoses. Many patients will exhibit a variable amount of desquamation after the rash fades, beginning about the fifth day. A brownish discoloration of the skin will persist for about seven to ten days.

If the physician suspects that the disease might be present, the diagnosis is usually not difficult and can often be anticipated in the prodromal period. If the examiner and the family are not aware of a possible exposure and the patient happens to be one of the first seasonal cases in the area, early diagnosis may easily be overlooked before occurrence of the rash. In some instances there may be considerable variation in the time of appearance of one sign or symptom in relation to the others. Another source of difficulty is an erroneous history of previous measles. In many instances, an apparent previous incidence, not to mention so-called second or third attacks in children, is actually German measles, exanthem subitum, or ECHO virus disease, which has been improperly diagnosed—usually, but not always, without aid of medical assistance. If the prodromal symptoms are nonspecific but alarming, the patient may even be hospitalized, and a day or two later, to the embarrassment of the physician and the annoyance of the ward personnel, the typical rash will develop.

The respiratory symptoms with hacking cough, the absence of pulmonary localizing signs, the conjunctival inflammation, and puffiness of lids and face will often give a clue to the diagnosis. Koplik spots, however, may be missed in artificial light or may be confused with food particles, thrush, aphthous stomatitis, and normal epithelial pearls. In poor light the early faint skin lesions may be overlooked. If the patient is seen in the home after daylight, it is often wise to conduct the examination in the kitchen if possible, since the housewife usually has good illumination in her "workshop" if nowhere else. A number of children are prone to develop intense mottling of the skin with hyperpyrexia, which can also be confusing. It should also be kept in mind that drug and serum reactions and viral infections such as rubella, exanthem subitum, and ECHO virus infections can manifest with morbilliform eruptions. Occasionally scarlet fever will present initially with a blotchy rash on the arms and legs.

The uncomplicated case of measles usually

requires little more than symptomatic treatment. Nevertheless, the treatment should be definitive to give the patient maximum relief. Once the diagnosis is made, it is often wise to give the parents a brief but adequate description of the disease. This is particularly important when it is the family's first experience with the disease, since the clinical course in each patient is unpredictable. Measles is often considered lightly by the laity, and if a child develops a typical but rather prostrating infection, the normal anxiety may easily lead to panic if the parents are not alerted somewhat to the nature of the symptoms, their possible severity, and their usual time relationship. Moreover, such briefing will help the parents make early and intelligent use of further medical consultation if complications arise.

At the height of the disease, the temperature may remain at a level of 104 to 105° F. for several days. This is usually satisfactorily handled with aspirin in appropriate doses every four to six hours for several days, tepid sponges, and baths. Once the rash is well out, the temperature drops rapidly to normal unless there is a complication. It has been said that warm baths or wrapping the child in blankets "brings out the rash." If so, it would not seem to be of much therapeutic importance.

The cough with measles is often the most distressing symptom for which the patient requires relief. It is hacking and nonproductive and can lead to exhaustion. The nonnarcotic antitussives in adequate dose are usually effective. If codeine is required, it should be administered in widely spaced doses. Oversedation should be avoided, since marked drowsiness so induced may be mistaken for the onset of a central nervous system complication. The parents should be instructed not to smoke in the child's room. The cough of measles may last one to two weeks, with diminishing severity. Some relief is probably obtained from steam inhalations.

If the patient experiences considerable itching and is troubled by the subsequent desquamation, an oral antihistamine together with an antipruritic lotion containing an oil applied topically may give relief. Simple cleansing of the eyes is usually sufficient, but if the conjunctivitis is severe and the lids become sticky and irritated with discharge, one of the antibiotic ophthalmic ointments can be used to advantage. Photophobia can be relieved with dark glasses, but precautions regarding light are seldom required.

Routine treatment with antibiotics for prophylactic purpose in uncomplicated cases is probably not indicated.⁸ It is wise, however, to pro-

tect the child with a chronic illness or one who is convalescing from a recent bacterial infection with appropriate antibiotics. The average patient with no complications is best treated in the home with reasonable isolation precautions for his own safety. The diet, room temperature, and general supportive care is normally no different from that required by patients with other self-limited, acute, febrile, respiratory diseases.

Sustained fever after the rash is fully developed suggests the presence of a complication, most often an infection of the respiratory tract. Pneumonia may be present in about 10 per cent of cases. The child 2 years of age or younger is especially vulnerable during the winter and early spring months. It was this age group that contributed largely to the 30 per cent mortality in the preantibiotic era. Otitis media, laryngitis, and cervical adenitis are less frequent causes of morbidity. Prompt use of appropriate antibiotic and additional supportive care have reduced the mortality from these complications to a minimum.

The younger child is also vulnerable to the severe form of measles which may develop at the height of an epidemic. The onset may be abrupt with sustained temperature to 105° F., accompanied by convulsions, delirium and stupor, or meningeal signs. The skin becomes mottled, dehydrated, and cyanotic, and the patient may die before the rash occurs or is fully developed. Occasionally the disease may run a typical course until the midpoint of the exanthem, at which point it overwhelms the patient. The rash may become hemorrhagic, and purpura, accompanied by bleeding from the gastrointestinal tract, may develop. Occasionally, circulatory failure will occur.

The diagnosis of giant-cell pneumonia has heretofore been usually based on retrospective histologic studies. The clinical diagnosis, however, must depend on isolating the virus and establishing its identity by the likeness of cytopathogenic properties to those of the measles virus. If no rash is present, and where laboratory facilities for viral diagnosis are not available, the clinical diagnosis of giant-cell pneumonia can only be surmised in the exposed patient with chronic debilitating disease in whom an intercurrent viral type of pneumonia develops.

Every patient with an overwhelming measles infection requires admission to the hospital for prompt and intensive supportive treatment. Although gamma globulin is of doubtful value in most instances, seriously ill patients deserve the possible benefit that might be derived from the

prompt administration of large doses. Treatment with measles convalescent plasma, as well as large doses of gamma globulin, has been reported to be lifesaving in giant-cell pneumonia.

Measles has a deleterious effect on the course of tuberculosis; primary tuberculosis may progress in a child recovering from measles. This is not apt to occur, however, in the patient who is receiving chemotherapy.⁹

In the child who normally enjoys good health, measles encephalitis offers the most serious potential for death or disability. Encephalitis may occur at the onset of measles as a result of direct invasion of the brain by virus, but this is rare. Measles encephalitis usually develops from three to six days after the rash, and patients are practically all under 13 years of age. There is no relationship between the severity of the disease and the frequency of the complication, which occurs in about 1 of 600 to 1,000 cases. More cases are observed in years of greater incidence of measles.

In measles encephalitis there is always some disturbance of consciousness, but the drowsiness and lethargy may not be pronounced and can subside in a few days. The disease may be ushered in, however, with headache, fever, vomiting, irritability, transient staring episodes, rolling of the eyes, diplopia and nystagmus, hallucinations, and disorientation. These may be followed by coma or convulsions or alternating periods of both. Occasionally the complication is characterized by tremor, choreiform and athetoid movements, aphasia, and hemiplegia. If the medulla and pons are involved, bulbar paralysis with respiratory and circulatory failure may ensue.

There is apparently no consistent correlation between the number of cells in the cerebrospinal fluid and the severity and outcome of the illness. The cells may number from less than 20 to several hundred, usually with a majority of lymphocytes. The proteins may be normal or increased and the sugar content is not constant. An isolated febrile convulsion during the prodrome of measles, especially if accompanied by a normal spinal fluid, usually is benign, and the disease can progress without further evidence of nervous system involvement.

The patient with encephalitis who does not go beyond the point of drowsiness or lethargy from which he can be aroused will usually recover with ordinary supportive treatment. If the patient is sufficiently awake to swallow, nutrition and hydration can be maintained with spoon feeding if necessary. Sedative drugs should not be given, for they add to the depression of con-

sciousness and make it more difficult to follow the course of the primary brain disease. In the milder case, rectal administration of a simple aspirin-phenacetin-caffeine combination often relieves headache and nausea. For example, two 5-grain APC tablets or capsules are lubricated and inserted into the rectum of a 5 year old every six to eight hours for 2 or 3 doses.

Effective treatment of severe encephalitis requires the presence of hospital personnel and attendants who are experienced in the use of the tank respirator, maintenance of airway, and other nursing procedures necessary for the survival of the critically ill, stuporous, or comatose patient who is frequently a candidate for respiratory failure. The supportive treatment of the comatose patient should begin as soon as possible. Asphyxia is especially dangerous in the patient with inflammation of the brain because of the increased oxygen requirement. If the airway is not adequately maintained with frequent nasotracheal suction, an endotracheal tube may need to be inserted or tracheostomy performed. Anoxia adds further to the central nervous system depression, and one should not wait for cyanosis to develop by reason of slowed or shallow respiration before using the respirator.

Fluids and salt should be administered intravenously but only in amounts just sufficient to cover minimal requirements so as not to increase cerebral edema. After the acute period, nutrition can be maintained by tube feedings. Adrenocortical extract may be given to patients in collapse. A vasopressor agent, such as levarterenol (Levophed) bitartrate, can be added to the intravenous solution if arterial hypotension develops. Cardiac irregularities may require specific treatment. Hyperthermia is best treated with cold packs, alcohol-soaked sheets, fans, and tap water retention enemas and by keeping the oxygen tent cool. An indwelling catheter is often indicated. The patient should be turned frequently to prevent hypostatic pneumonia. Sodium phenobarbital can be administered intramuscularly or intravenously to control seizures. If the patient has marked respiratory difficulty, the aim should be to decrease the frequency of the seizures to prevent exhaustion but without further depressing the vital functions. In such instances diphenylhydantoin (Dilantin) sodium, given at six-hour intervals, may allow the use of smaller amounts of phenobarbital.¹⁰

The benefit of corticosteroid therapy, previously reported to be effective in the treatment of measles encephalitis, has not been confirmed according to recent studies. If postinfectious encephalitis actually occurs as the result of a hy-

perimmune response, irreversible changes probably develop shortly after the initial symptoms of encephalitis appear. To be effective corticosteroids would have to be administered before the encephalitic symptoms begin. Ziegra¹¹ reported a control group of 32 cases in which he could demonstrate no apparent benefit related to corticosteroid therapy. Karelitz and Eisenberg¹² in a series of 42 cases found that the administration of corticosteroids did not prevent nervous system complications and questioned the advisability of their use in measles encephalitis. McLean,¹³ however, of the Hospital for Sick Children at Toronto, believes that more rapid improvement is followed by the use of corticosteroids. He administers hydrocortisone in the dose of 4 mg. per pound of body weight per day until definite improvement is shown and consciousness is regained. From the evidence at hand to date it would appear that corticosteroids are of doubtful value in this disease. Until its therapeutic value is definitely disproved, however, there should be no criticism if the physician desires to use corticosteroid in the acutely ill patient who is faced with a life-threatening situation in which about 10 per cent so affected die. It should be stressed again, however, that it is the prompt effective supportive measures which often permit recovery that might otherwise not take place.

Improvement and recovery is usually rapid in the patient who recovers completely. The patient may emerge from coma, his convulsions may cease, and he may become afebrile in one to three days. A patient may remain stuporous for several weeks, and after regaining consciousness, mental confusion, disorientation, loss of memory, speech disturbances, personality changes, and even hemiplegia may be present and persist for a variable period of time. Nevertheless, the patients may still go on to complete recovery. About 20 per cent of patients suffer permanent disabilities including behavior changes, mental deterioration, visual and hearing defects, and epilepsy. Irrespective of the initial severity of the disease, the extent of permanent brain damage is unpredictable.

The patient with measles is considered contagious during the time his catarrhal symptoms are present and usually ceases to be so after the fifth day following the development of the rash, normally coincidental with the time the patient also becomes afebrile. Exposure is usually by direct contact, but a third person, who comes directly from the patient, may possibly be a source of infection to another in the same building. An individual is considered susceptible unless he

has had measles or has received an immunizing injection of gamma globulin within the last four weeks. An infant born of an immune mother is immune to the age of 6 months. Susceptible contacts in most areas are allowed to remain in school until several days before the prodromal period, since it is doubtful that rigid quarantine regulations accomplish very much. A child exposed at home, however, should not be allowed to expose a nursery school group.

The only known source for protective measles antibodies is human blood. The antibodies are available in the forms of convalescent serum, parental serum and whole blood, gamma globulin, and placental extract. Before gamma globulin became available, it was customary to give 5 to 10 ml. of convalescent serum or 15 to 30 ml. of parental serum intramuscularly into the buttocks within six days of exposure.

Measles can be prevented or attenuated by gamma globulin, which is a concentrated solution of the antibody-bearing globulin fraction derived from pooled normal human blood plasma. Each milliliter contains the antibody equivalent of 25 ml. of original plasma obtained from many adult donors. There are 2 commercial preparations presently available for therapeutic use. One is immune serum globulin, U.S.P. (human), and the other is poliomyelitis-immune globulin (human). Both are the same except that the latter preparation has been specifically demonstrated to meet a standard set by the National Institutes of Health for content of Type 2 (Lansing) poliomyelitis antibody.

Concentrated gamma globulin should only be given intramuscularly or subcutaneously. Accidental intravenous administration may cause severe cardiac arrhythmia, hypotension, and hyperpyrexia. Intramuscular injection provides a peak serum level by the second day after injection. The antibodies remain stable in gamma globulin for long periods, and the commercial preparations have not been known to transmit serum hepatitis and are rarely the cause of toxic or allergic reactions.¹⁴

Every healthy nonimmune child deserves the protection of an attenuating dose of gamma globulin. Attenuation reduces the number of complications and not only reduces the prevalence of encephalitis but also diminishes the severity of an attack if it should occur. Attenuation can usually be accomplished in a majority of children with a dose of 0.02 ml. per pound given during the first six days after exposure. After the sixth day of exposure, the recommended dose for attenuation should be doubled and may be effective in modifying the disease when given as

late as the appearance of Koplik spots but not after the rash appears. Attenuated measles is characterized by a longer incubation period (up to nineteen days) and mild symptoms with minimal rash. The majority of children who experience a mild case of measles as a result of receiving an attenuating dose develop a lifelong immunity. It has recently been demonstrated that susceptible children protected with an attenuating dose of gamma globulin develop antibodies even when there are no overt signs of disease.¹⁵ The child with modified measles is contagious if catarrhal symptoms are present.

Complete prevention of measles can usually be attained with gamma globulin by a dose of 0.1 ml. per pound of body weight given during the first six days after exposure. After the sixth day, twice this dose may be effective. Prevention of measles is indicated in children under the age of 2 years and in patients with concurrent illness, such as fibrocystic disease, tuberculosis, or other debilitating disease. It is wise to give a preventive dose to the nonimmune pregnant woman to minimize the possibility of premature labor or abortion. All patients exposed in a hospital ward should receive a preventive dose of gamma globulin. Passive immunity so attained lasts three weeks.

An introduction to the recent developments in the achievement of active immunization against measles has been most adequately summarized by Dolgin and associates.¹⁶ He wrote:

"... progress in measles prophylaxis has been greatly delayed for many years because of the absence of a simple technique for detecting virus multiplication. Shaffer, Rake, Stokes, and O'Neil, in 1941, propagated what was believed to be the measles virus in the chick embryo, but they were unable to demonstrate any cytopathogenic effects in the embryonic tissue. Material that had undergone serial chick embryo passage was then inoculated into monkeys and children. Mild but definite measles is reported to have occurred in several of the children as well as in the monkeys. The results on the whole were, however, inconclusive and suffered from the lack of an available method for demonstrating infectivity, viral multiplication, and antibodies.

The obstacle was finally removed in 1954 when Enders and Peebles were successful in demonstrating cytopathogenic effects⁹ of the measles virus in tissue culture. They also demonstrated that antibodies, developed in the serum of patients recovered from measles, could be measured by the ability to prevent these cytopathogenic effects. This fundamental contribution made available the tools for studying the effects of the measles virus in man on a scientific basis. One additional difficulty, however, still remained. Enders and others have pointed out that human cells may carry the risk of introducing latent virus potentially pathogenic for man and, therefore, would be hazardous if used in the preparation of a

⁹The development of characteristic multinuclear giant cells in tissue culture of human and monkey renal cells as result of viral multiplication.

vaccine. The proteins of the chick embryo, however, are well tolerated by human beings, as is proved by the large-scale use of yellow fever and influenza vaccines. After Enders and Peebles demonstrated propagation of the measles virus in primate cells by the tissue culture technique, it was not long before it became possible to demonstrate propagation of the measles virus in chick embryo tissue culture."

The adaptation of measles virus to chick embryo cell cultures provided a means of developing an attenuated live virus vaccine.¹⁷ Encouraging results in experimental animals led to its use in human trials. From the reports of investigators it would appear that the attenuated vaccine has a highly protective effect against measles. The subjects inoculated in experimental studies developed mild to moderate symptoms, presumably did not become infectious, developed no bacterial or neurologic complications, and developed sufficient antibodies to withstand subsequent challenge to the disease. Although the illness produced by the vaccine is not serious, it has been sufficient to cause workers to seek some modification of the vaccine. This has been achieved by combining the live attenuated virus vaccine with gamma globulin.

Some objections, however, have been raised with regard to the feasibility for general use of the attenuated virus vaccine despite the modification with gamma globulin. It has been stated that the live virus vaccine is not stable and is adversely affected if not carefully refrigerated. Batches of gamma globulin vary in antibody content, and this introduces additional requirements for standardization. Not only would addition of gamma globulin increase the cost of the vaccine, but also the availability of gamma globulin might pose a problem.

Recently, Feldman¹⁸ and Winkelstein¹⁹ and their co-workers, in 2 separate studies, described their experiences with an inactivated measles virus vaccine. The vaccine was prepared from virus cultivated in monkey-kidney cells, concentrated and inactivated with formalin, and alum was added as an adjuvant. These reports indicate that the inactivated virus can stimulate a protective antibody response. They demonstrated that total protection may result from immunization and that only a mild disease occurs on subsequent exposure even if an inadequate amount of vaccine is used. It was also found that several months after inoculation with the inactivated virus vaccine the antibodies fell to undetectable levels. Despite this, when subjects were challenged by attenuated live virus, the modified illness failed to develop. The latent antibody response apparently also provides protection against the natural virus.

Advantages claimed for the inactivated virus vaccine are that it is exceedingly stable and retains its potency for a long period; it can be mixed with other nonviable antigens, such as those present in diphtheria-pertussis-tetanus or poliomyelitis vaccines, permitting it to be employed in immunization schedules now in current use; and finally it does not require the addition of gamma globulin as does the attenuated live virus vaccine.

Regardless of which type of vaccine is finally adopted for general use, it would appear that a safe and effective prophylaxis against measles should be available soon. This should eliminate the 500 to 600 deaths attributed to measles each year in the United States, as well as the serious sequelae arising from the complications involving the respiratory tract and the brain.

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Alma T. Hovde, R.N.

MARY A. JOHNSON, R.N.

Minneapolis

ALMA HOVDE retired in January 1960 from the directorship of the Rural Hennepin County Public Health Nursing Service after twenty-one years with that agency. That fact is noteworthy in itself.

The story of Alma Hovde's life and contribution to nursing parallels several important advances in public health practices within this state. The experiences of this pioneer nurse may be echoed in the lives of many of her contemporaries in the nursing field, as well as by the physicians who initiated public health programs throughout Minnesota.

When Miss Hovde began her career, the public health nursing course at the University was relatively new, and agencies necessarily were recruiting nursing staff first and then giving them on-the-job training to carry out the agencies' programs. Formal university education was encouraged later, when nurses decided to remain in public health work.

"Stop at Benson, where you will meet with Dr. C. L. Scofield. He has arranged for a group of women to listen to your talk and demonstration. Dr. Scofield, as a member of the Minnesota State Board of Health, is interested in the whole maternal and child health program being introduced through the Minnesota Department of Health. He may wish to give suggestions on your demonstration. After you have cleared with him, proceed on your schedule." With these parting instructions from the direc-

tor of the Division of Maternal and Child Health of the Minnesota Department of Health, Alma Hovde began her career in rural public health work, pioneering in the educational program provided by the recent passage of the Sheppard-Towner Act.

Her year of experience with the Infant Welfare Society of Minneapolis immediately after graduation from the Swedish Hospital School of Nursing in 1922 gave Miss Hovde background information in teaching the principles of breast feeding, the knack of breast expression, and the intricacies of formula preparation. Every day there were new faces in new places: young girls, young mothers, grandmothers, housewives, teachers, ministers and priests, home demonstration agents, county agents, farmers, and businessmen. The meeting place might be a school house, a village hall, a library, a church, or a private home. No matter where, Alma Hovde found people interested and eager for maternity dress and layette patterns and practical suggestions for providing sterile supplies for home deliveries. Those were the days when more than 60 per cent of deliveries took place in the home. Occasionally, a grandmother would ask, "How can you stand up before a crowd and talk about such personal matters?" For the answer to that question, we can go back to Alma's early life experiences.

THE MAKING OF A NURSE

Alma Hovde was born February 9, 1893, and grew up in a rural community near Hanska in Brown County. As 1 of 9 sisters and brothers living on a

MARY A. JOHNSON is administrative assistant, Section of Public Health Nursing, Minnesota Department of Public Health.

farm, she had learned to share responsibilities in housework and the care of younger children. She also had shared in the outdoor duties of gardening and the care of farm animals. She learned to appreciate the extra pressures upon families during the busy seasons of haying and harvest. As Alma said, "We all helped in the hayfield."

Alma Hovde's high school education in a church-sponsored school included preparation for rural teaching. Being selected as valedictorian of her class gave Alma her first sense of leadership and the responsibilities associated with being a leader. Four years of rural teaching gave her not only an understanding of children but also a sympathetic, easy rapport with parents. These experiences in early life, combined with an unusually strong desire to serve people, influenced Alma to go into nursing, and from there she gravitated toward a public health nursing career. Alma explains that a public health nurse living at the Hovde home while Alma was enrolled as a student nurse encouraged her to try public health nursing. Alma says, "That nurse made me curious."

After a year or more on the Minnesota Department of Health staff giving talks and demonstrations on maternal and child health, Miss Hovde decided she would like to get closer to families than she could in the group teaching program. Also, Miss Hovde wanted to visit western states. The Washington State Tuberculosis Association was most happy to place Miss Hovde on its payroll. The work took her into the schools for several months. When the assignment ended, Miss Hovde decided to enroll at the University of Washington in a public health nursing course. With a public health nursing certificate in her pocket, Miss Hovde decided to visit California. Because her nursing companions were occupied with hospital nursing, she decided to work in hospitals and as a private duty nurse while she was testing the lures offered by Hollywood and Los Angeles. After a few months, Miss Hovde decided she preferred the Midwest.

SCHOOL NURSE

Home again in Minnesota, Miss Hovde was employed as the first full-time school nurse in Edina. Diphtheria antitoxin was just being made available. It was a new idea to many parents. With a true pioneer spirit, Miss Hovde encouraged the Parent-Teacher Association to sponsor an information program. Dr. Aichard Olding Beard of the University of Minnesota was requested to explain the possibilities for community-wide protection from diphtheria through the use of antitoxin. Community leaders were convinced. Soon volunteers were at work with the health officer and the school nurse to carry out

one of the first diphtheria antitoxin immunization programs for school children in Minnesota.

Alma Hovde was about to pioneer in another public health venture, but she did not suspect it—not until her second year as the Edina school nurse. Suddenly, without fanfare or much warning, Alma found herself propped in bed listening to fellow patients in Glen Lake Sanatorium. No doubt there were many blue days, but, as a whole, those two years at Glen Lake Sanatorium gave perspective to Alma's interest in a public health nursing career. The kindness and masterful care extended to her from physicians, nurses, and rehabilitation workers made her realize more than ever that, working as a public health nurse, she would be able to extend this program of treatment and prevention of tuberculosis into many homes. But first, she must prove that she could hold her own and that she was not a health hazard.

At the time Miss Hovde was discharged from the sanatorium, employers were reluctant to hire persons who were obliged to work in easy stages. Surgery for appendicitis and again for an infected gallbladder further complicated convalescence and made job hunting difficult. It was at this point that Miss Hovde came to the Minnesota Department of Health for counseling. She reasoned that, once she had made the hurdle of being employed again as a public health nurse, her rehabilitation would be established. Fortunately, there was an opening for a school nurse in the Minnesota State School for the Blind—fortunately, because the director of that school believed thoroughly in the whole program of prevention, treatment, and rehabilitation for tuberculous patients. He expressed this belief by employing Miss Hovde as the school nurse, knowing that she would remain only until a broader opportunity in public health nursing was available to her.

Within a few short months, Miss Hovde was offered the school nursing position in Columbia Heights. The location enabled her to take extension classes at the University. Summers were free to take additional University courses or to get the extra rest needed to build up her endurance. It was while Miss Hovde was working in Columbia Heights that a highly successful pilot tuberculin testing program was initiated for the high school population by the board of education and local physicians. The teachers in the general science classes developed a pilot teaching unit on tuberculosis control, incorporating the tuberculin test and its interpretation into the content. Every pupil enrolled in the pilot study group was tested.

PUBLIC HEALTH

After six years in the Columbia Heights Schools, Miss Hovde decided that it was time to round out

her public health nursing experiences by working with an agency that included nursing services to all members of families. An opening on the Hennepin County nursing staff in 1939 offered this opportunity. This position included serving as a field teacher for public health nursing students who were being assigned by the University to Hennepin County for a part of their instruction in public health nursing. Four years of experience as a staff nurse culminated in her promotion to the directorship in 1943. Shortly thereafter, an educational leave was granted to permit Miss Hovde to meet requirements for that coveted Bachelor of Science degree in public health nursing.

We all remember the chaos that resulted from depleted nursing staffs during the war years. The Hennepin County Public Health Nursing Service was no exception. Alma Hovde's pioneer spirit helped meet the many crises that seemed unending. She encouraged staff nurses to call more extensively on volunteers and to give them the guidance necessary to carry out their assignments. This philosophy of orienting the volunteers throughout the county brought lasting rewards, because every community leader and volunteer knew the goals of the nursing service and came to its rescue when a special bill was passed in 1951 which prevented the Hennepin County Public Health Nursing Service from receiving financial support from the general revenue funds of the county. Practically every community in rural Hennepin County rallied to the support of taxes in townships and municipalities necessary to retain the public health nursing service.

It took stamina on the part of the nursing staff, as well as the newly organized nursing board, to keep working in the face of such uncertainties as not knowing whether or not there would be money to cover the pay checks. The fact that Miss Hovde never wavered gave stability and a feeling of confidence to the nurses, to the board members, and to those valiant auxiliary nursing committee members who worked together not only to retain the nursing service but to be able to meet the changing public health nursing needs.

When Alma Hovde retired in January 1960, she could visualize what may develop within the Hennepin County Rural Public Health Nursing Service. For many years, the service had consisted of 5 or 6 nurses, as it had when Miss Hovde joined the staff. At the time she retired, the number had grown to 14 nurses and 3 clerical workers, with the momentum building up for ever-greater expansion.

Alma Hovde gives credit for this growth to the many dedicated citizens who have supported the public health nursing service for rural Hennepin County. Many of these persons were members of the auxiliary nursing committees; others were members of the administrative board—even before Miss Hovde was employed on the staff; others have been persistent workers on the current administrative board. Persons no longer counted as members of the agency continue to respond whenever their support is needed. Many professional persons have given their support and guidance through the Hennepin County Health Council.

As Miss Hovde further expresses her feelings about her career, she is appreciative of having played a part in the great humanitarian profession of nursing, but, in particular, there is an especially deep satisfaction for the rich experiences gained in public health nursing.

And how does a nurse retire from a career of public health nursing administration? Miss Hovde now has time for travel, which hitherto she has been able to do only in snatches. This summer she has been visiting in the Scandinavian countries, Germany, France, and England, renewing acquaintances with nurses who have been in Minnesota on travel scholarships. When she is at home, Alma Hovde finds many opportunities to lend a hand—with church groups and altruistic organizations. So far she has had little time to reminisce—or to pursue her other hobbies of knitting and photography.

Alma Hovde finds that one of her greatest pleasures since retirement comes when she realizes she now has time to take part in neighborhood and church activities, and no two days of events seem to duplicate each other.

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¹ Ford, R. A., and Blanchard, K. *Journal Lancet* 78:185, 1958.

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Book Reviews . . .

Postoperative Care in Thoracic Surgery

HENRY J. HEIMLICH, M.D., 1962. *Springfield, Ill.: Charles C Thomas. 44 pages. Illustrated. \$4.25.*

Professor Heimlich states in his preface that this booklet on postoperative thoracic problems is designed for nurses, interns, and residents. He presents a very simple, easy to follow sketch of the difficulties seen by the nurse in the postoperative intensive care unit. The prose used by Dr. Heimlich is sometimes redundant, possibly due, I feel, to a lack of intensive proofreading before final publication.

I have used the diagrams in this booklet to good advantage in instruction of nurses and intend to reproduce a few of the pictures for slide demonstrations.

Aside from the most concise discussion of chest suction apparatus, the booklet, in my estimation, is somewhat below the level of surgical resident intelligence. Nevertheless, it is a most worthwhile instruction manual for the student, intern, and surgical nurse.

SAMUEL W. HUNTER, M.D.
St. Paul

General Pathology

SIR HOWARD FLOREY, *editor, third edition, 1962. Philadelphia: W. B. Saunders. 1104 pages. Illustrated. \$22.00.*

Lectures delivered at the Sir William Dunn School of Pathology, University of Oxford, serve as the basis for this valuable text. The format is similar to that of the earlier editions, but there has been fairly extensive revision. Papers by 17 authors are included.

Principles in general pathology are covered in a thorough manner under 44 chapter headings. The book does not attempt to cover the entire field of pathology, however, and there is very little special or organ pathology included. Tumors are covered in a general way, with examples of major groupings according to cell type.

Those subjects which are considered are thoroughly discussed in a readable style. For example, the subject of pathogenicity and virulence of microorganisms is dealt with in 4 chapters. The chapters on anaphylaxis and allergic disorders of man are excellent.

Photomicrographs are used to advantage throughout the text and these are of uniformly fine quality with concise legends. Especially noteworthy is the abundant use of electron micrographs; an excellent series of these is in the chapter on inflammation.

This text is highly recommended for those who are interested in developing a deeper understanding of the principles of general pathology. It is particularly useful for those at graduate level and beyond.

RICHARD P. LYNCH, M.D.
St. Paul

Structural Forms of Anesthetic Compounds

HUGH S. MATHEWSON, M.D., 1961. *Springfield, Ill.: Charles C Thomas. 223 pages. Illustrated. \$6.75*

The past two decades have seen an expanded and a progressive increase in the understanding and application of many of the basic fundamentals of physiology,

pharmacology, and biochemistry as they pertain to the field of anesthesiology.

The amount of current literature and the complexities of modern concepts make it increasingly difficult for the teacher, the graduate student, the medical student, and the beginning investigator to keep abreast of all of the knowledge in any one field. It is even a considerable task for a student to start a review of a subject or to begin a penetration into depth of a single field.

If this newer knowledge is to be useful to those who are not yet specialists and even, to a degree, to those who are highly trained in a specialty, it must be collected, selected, and organized so that it presents a systemized whole. It must be fitted into contexts of accepted facts and placed in proper perspective.

The American Lecture Series monogram in anesthesia entitled, "Structural Forms of Anesthetic Compounds" by Hugh S. Mathewson, admirably fulfills such a need in anesthesiology. It attempts to relate the reactions of anesthetic drugs to chemical structural activity. As stated in the preface of the book, the structural formula of a compound embodies many physicochemical characteristics and, therefore, often earmarks a drug as belonging to a certain classification.

This text will serve a primary objective in the teaching of medical students and residents in anesthesiology. The well-written text gives many useful correlations that can be drawn and remembered by reference to structural similarities and differences, which are amply discussed and illustrated throughout the book. From the viewpoint of the student, the basic fundamentals of modern anesthesiology are presented in a manner that greatly facilitates the orderly introduction of anesthetic agents through structural activity principles.

This 20-chapter book is arranged so that the more commonly used anesthetic drugs and agents receive the most emphasis. However, many ancillary drugs, though not classified as anesthetic agents or drugs but used in clinical anesthesiology, are also elaborated upon.

Though the author is aware that chemistry, even for the students of anesthesiology, can be a tedious affair, he does not apologize for it. The text is written and organized so that it is not only of interest to anesthesiologists or those who intend to enter the field of anesthesiology but also to all physicians who deal with depressant and potent drugs. This is further illustrated by the fact that this book, by virtue of its function in classifying the activity of many drugs on a structural basis, can enhance understanding of the structural activity and, hence, of the untoward side reactions, thereby guiding the physician to a more judicious selection and use of drugs.

IRVING GREENFIELD, M.D.
Minneapolis

Electrocardiography

E. GREY DIMOND, M.D., PAUL SCHLESINGER, M.D., and RAFAEL L. LUNA, M.D., *Third edition, 1962. Mission, Kansas: The Corinth Press. 196 pages. Illustrated. \$6.00.*

The purpose of this book is to discuss spatial electrocardiography and vectorcardiography from a clinical point of view. This monograph is intended for the

(Continued on page 14A)

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BOOK REVIEWS

(Continued from page 12A)

student or the practicing physician and is primarily a teaching method, not a reference text or treatise.

The authors have divided the book into 4 sections: Section I develops fully the basic physiology of vectors, leads, and spatial analysis. Section II presents concepts of ischemia, injury, necrosis, hypertrophy, overloading, and block. Section III presents actual records, with detailed analyses of the electrocardiogram and vectorcardiogram, employing information from sections I and II. Section IV presents, in alphabetical order, definitions or descriptions pertinent to the general subject of electrocardiography.

The discussion covers the important features of the subject and is well illustrated with simple figures which add a great deal to the value of the book. The authors have had considerable experience in teaching this subject; they discuss the various points lucidly and have well accomplished their original aims.

This atlas is recommended for use by students and practicing physicians as an adjunct to other texts in electrocardiography and vectorcardiography.

SAMUEL BELLET, M.D.
Philadelphia

Pharmacology and Therapeutics

ARTHUR GROLLMAN, PH.D., M.D., *fifth edition, 1962.*
Philadelphia: Lea & Febiger. 1131 pages. \$12.50.

In the two-year period since the fourth edition of this work, it may be estimated that about 800 new drug products or 100 new chemicals have been developed. Hence, a current revision is needed and, in general, Dr. Grollman has succeeded in bringing his book up to date.

The section on thyroid, for example, is clear, simple, and current enough to include a group of cholesterol-lowering compounds which are only now being reported in the clinical literature. These are mirror-image analogues of the thyroid hormones, D thyroxine and D triiodothyronine, alleged to exert their clinical effects without cardiac stimulation.

Dr. Grollman does as well with the psychotherapeutic drugs, currently at the peak of their popularity and producing a welter of advertising mail with conflicting claims and confusing pharmacodynamics. There is a fine section on serotonin, its role in carcinoid tumors, its reciprocal relation to reserpine, and its relation to mood therapy.

On the negative side, his chapter on digitalis is uneven. While the introductory section on the chemistry of the glycosides is excellent, his description of the mechanism of the action of digitalis is too brief and hard to follow. Similarly, the chapter on alkylating agents could be simplified, possibly by illustrations. As it is, some paragraphs bristle with allusions to unfamiliar chemical processes. Also, his discussion of chelating agents is disappointing. Only 3 paragraphs are given to an increasingly useful method of removing toxic metals from the body, particularly lead, iron, and copper (as in Wilson's disease).

In sum, this is a good book that can be improved. One of its chief merits is its brevity, but for medical students it may be too terse, with slighting of important items. Typographically, this book is attractive, using boldface type for emphasis in the text and having ample headings and spacing. I would recommend this book for all practicing physicians as a ready reference.

FRANK ANKER, M.D.
Oakland, California

BOOK REVIEWS

Rehabilitation Codes

MAYA RIVIERE, PH.D., *director, 1962. Sponsored by The Association for the Aid of Crippled Children. New York: Rehabilitation Codes. 174 pages. Available at no charge to professional workers.*

Information vital to the complete rehabilitation process, in the form of an illustrious and highly developed system of classifications, can now be expressed in a common language through the "New Rehabilitation Codes." This most modern and revolutionary breakthrough in communications, heretofore completely underdeveloped in the field of physical medicine and rehabilitation, will serve with excellence in the comprehensive agency. However, the small agency which is preoccupied with a single discipline will accept this not as a guide or as an operational tool, but rather as an elaborate, costly, and cumbersome system requiring batteries of electronic computers to serially record the rehabilitation process. No agency can know everything, nor would it seem absolutely necessary to know all that there is to know about a patient or a client who needs help from the specialty of rehabilitation. The master lists for total and complete identification endeavor to be too inclusive for all of man's many and varied dimensions. Many professional rehabilitation workers and agencies simply sit around and wait for voluminous reports before taking some positive action. The experts in rehabilitation must overcome a most serious problem if this coded system can be truly effective. The lack of interagency cooperation in our land will prevent this orderly arrangement and organization of data from becoming widely accepted and utilized.

R. J. RABIDEAU, R.P.T., R.N.
Virginia, Minnesota

Vector Electrocardiography

HERMAN N. UHLEY, M.D., 1962. Philadelphia: J. B. Lippincott Co. 339 pages. Illustrated.

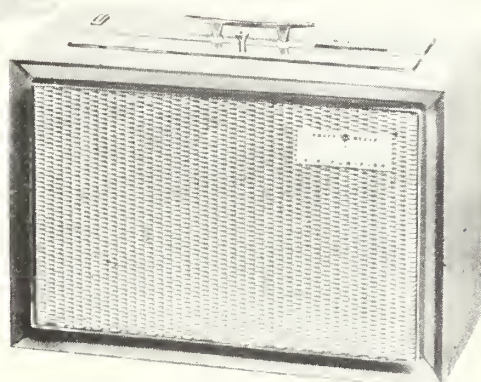
Dr. Uhley, in this monograph, has attempted to bridge the gap between vectorcardiography and electrocardiography in a manner which will be understandable and of practical use to clinicians. Students of vectorcardiography may find the presentation too simplified and brief. The author has, however, succeeded in making vectorcardiography and its relationship to the standard electrocardiogram intelligible to the practicing physician. Abnormalities in the standard electrocardiogram produced by heart disease become much more meaningful when changes occurring simultaneously in the vectorcardiogram are also understood.

The concepts of vector electrocardiography are presented concisely and clearly and with a large number of illustrations, so that the evolution of vector spatial loops and resulting electrocardiogram complexes can be easily followed. The illustrations are well done and the author has utilized a method of illustration in which by flipping the pages the effect of animation is produced and sequential changes in the vector spatial loop and standard electrocardiogram leads can be visually followed. However, even in this simplified form, the subject matter is complicated and the material must be carefully studied and reviewed. The book includes a brief description of the normal vectorcardiogram and electrocardiogram, and then by means of a combination of brief descriptive text and diagrams, the changes produced by ventricular hy-

(Continued on page 16A)

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BOOK REVIEWS

(Continued from page 15A)

pertrophy, ventricular conduction disturbances, and myocardial infarction are described. Discussion of theoretic concepts is kept to a minimum.

The author assumes considerable knowledge of standard electrocardiography on the part of the reader, thus making the text most useful to internists, cardiologists, and others with background in standard electrocardiography. Prior exposure to vectorcardiography is not necessary. Readers who have not had some training in standard electrocardiography will find this book difficult to read and perhaps incomprehensible.

ALVIN L. SCHULTZ, M.D.
Minneapolis

Accident Prevention: The Role of Physicians and Public Health Workers

MAXWELL N. HALSEY, *editorial consultant, 1961. New York: McGraw-Hill. 400 pages. Illustrated. \$12.00.*

The needs of the physician, the public health worker, and the schools of public health for a comprehensive publication in the area of accident prevention are met in this book. In addition to the familiar areas of industrial, traffic, and home safety, the text includes farm, recreational, institutional, and flight safety. The relationship of each to the duties and interests of the physician and public health worker is clearly presented. The problems associated with the very young and the aged are given special attention.

The 33 authors appear to have been selected because

of competence in their fields. It is unfortunate that the editorial consultant did not deem it his prerogative to delete many of the repetitious statistics and common safety axioms and to adjust the wordage on specific subjects to that subject's import in the entire area of safety. As a result, we have a satisfactory reference book with good bibliographies on each subject, but one that is tedious or almost impossible for cover-to-cover reading. However, the Editor's Note, Contents, and Index combine to provide a clear guide in using this book for reference in gaining knowledge and insight into many specific phases of safety.

Several chapters appear as outstanding contributions; included would be, "The Physician's Role," "Industrial Safety," and, although somewhat lengthy in relation to its role in the over-all field, "Private Flight Safety." Some other chapters are, unfortunately, only a collection of past experience, previous statements, and itemized rules, all presented without thoughtful analysis. Such information may be valuable reference material, but much is missing in the chapters "School Safety," "Recreational Safety," and "Programs for Physicians and Medical Societies."

Every present-day concept and theory relating to accident prevention appears somewhere in the text. Some contradict others, but all have reasons for their development. Safety has seen its past development through reason, not research. If reason is used in application and selection of the material in this text, it will become a valuable contribution to accident prevention.

The public health worker and, particularly, the physician would do well to add this book to their libraries.

GUSTAVE L. SCHEFFLER
Minneapolis



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Fractures of the Nasal Bones and Septum

JOHN B. ERICH, M.D.

Rochester, Minnesota

SINCE MOST UNTREATED FRACTURES of the nasal bones and septum produce some degree of deformity, it is regrettable that so many of these injuries are still being ignored or overlooked. When such fractures are neglected in persons who have not reached physical maturity, the resultant nasal deformity becomes increasingly more apparent as the child grows to adulthood. Although it is true that many abnormalities of nasal contour due to trauma cannot be completely corrected, there is no question but that many of these defects of the nose could have been avoided if more time had been devoted to the primary care of the injury.

TYPES OF FRACTURES AND TREATMENT

Fractures of the nasal region can be divided into three categories: (1) simple fractures of the nasal bones and nasal septum, (2) severe crushing injuries to the nose associated with fractures of the ethmoid bone, and (3) nasal deformities due to old fractures of the nasal bones and septum.

Treatment of simple fractures of the nasal bones and septum. The treatment of uncomplicated fractures of the nose is well known. The use of an elevator or other blunt instrument in each nasal cavity together with external finger pressure will permit manipulation of the fragments into proper position. One cannot over-

emphasize the need of restoring displaced fragments of the nasal septum to normal position, thus preventing not only external deformities but also obstruction of one or both nasal cavities. Septal fractures can be reduced with the aid of blunt elevators, one being inserted in each nostril; care should be taken to replace the septum on the crista nasalis and the septal cartilage on the anterior margin of the vomer bone. For immobilization, I prefer to use petroleum jelly (Vaseline) gauze packed tightly into each nasal cavity. In addition, an external metal splint, held in place with adhesive tape, is helpful. Fixation should be maintained for five to ten days. At the end of five days I remove the packs, suck the mucus out of each nasal cavity, and, often, repack the nose for another five days. In children, general anesthesia is usually required for careful and appropriate reduction and immobilization of the nasal fractures.

While discussing the care of simple fractures of the nasal bone, I would like to mention briefly the treatment of these fractures by the method of open reduction. This technic requires an incision in each nasal vestibule between the upper and lower lateral cartilages. Through these intranasal cuts, the skin covering the nose is freed from the underlying tissues. On retracting the undermined skin, one can inspect the displaced bony nasal fragments. Theoretically, these can be repositioned in normal alignment under direct vision; however, in my experience, the ultimate results of open reduction are no better than those that can be obtained by blind manipulation.

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Treatment of the severely crushed nose. Severe compression injuries of the nose are serious because they are invariably associated with fractures of the cribriform plate of the ethmoid bone. Consequently, cerebrospinal rhinorrhea is likely to be a prominent symptom, and there is some danger that meningitis will develop. The immediate treatment includes the administration of penicillin and perhaps one of the other antibiotics in an effort to prevent intracranial infection. Notwithstanding the fact that some surgeons have no hesitancy in treating these severely crushed noses without delay, it is my opinion that reduction of the fractures should be delayed

until the patient's general condition is satisfactory and until the drainage of cerebrospinal rhinorrhea has stopped, which is a matter of seven to ten days.

It is useless to elevate badly comminuted and depressed nasal bones unless some form of fixation is available for retaining the fragments in proper position. If the crushing injury has not caused too much depression, one effective method of therapy is to employ external lead plates through which are threaded stainless steel wires that pass horizontally through the nose (figure 1). Such plates and wires are not disturbed for ten to fourteen days; they not only narrow the bridge but also tend to push the nasal bones forward, thereby correcting the depression defect.

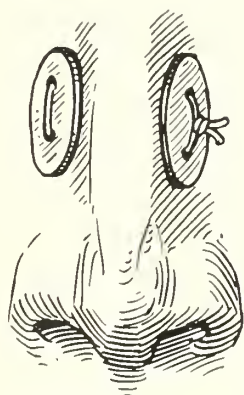


Fig. 1. Use of lead plates and a stainless steel wire for immobilization of depression fractures of nasal bones. This arrangement not only narrows bridge of nose but tends to bring it forward, thereby correcting depression defect.

If, however, the depression of the nose is especially severe, some mechanical contrivance must be inserted behind the nasal bones to hold them forward. Many appliances have been devised for this purpose. A simple method is to use wires through the nose which engage intranasal splints, as is shown in figure 2. When the wires are attached to a plaster headcap, they provide an effective means of holding the nasal bones in a forward position until healing has taken place. The stainless steel wire is inserted

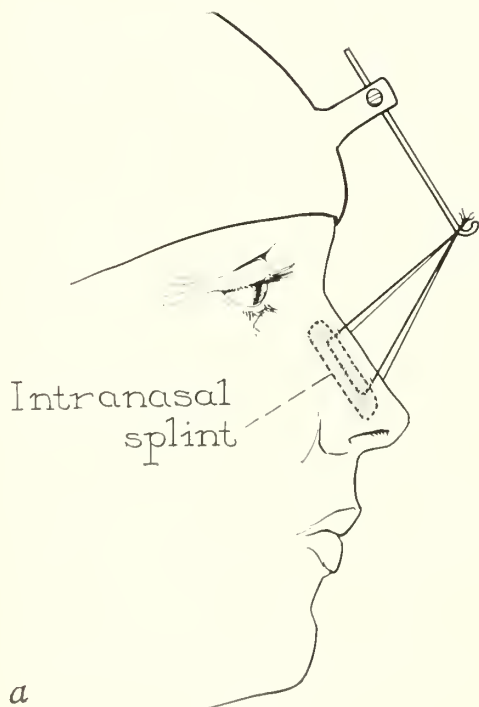


Fig. 2. *a.* Use of stainless steel wires passed through nose from intranasal plastic splints to a plaster headcap externally. This appliance effects satisfactory elevation of severely crushed nasal fractures. *b.* Appliance in position on a patient





Fig. 3. Distortion of fresh autogenous cartilage implant in nose due to unavoidable warping of cartilage.



Fig. 4. Exposure of crest of ilium to obtain bone for nasal implants

on either side of the nose by means of a curved cutting needle; it is passed through the dorsum of the nose into the nasal cavity, brought out through the nostril, threaded through holes in the acrylic (plastic) splint, carried back into the nasal cavity, and brought through the dorsum of the nose externally. The splints are then inserted behind the nasal bones in the nasal cavities; as the wires are made tense and attached to the plaster headcap, the nasal bones are elevated and immobilized. The appliance is left in place for at least ten days. Although any such apparatus may not correct the nasal depression completely, it is most helpful in preventing an irreparable deformity. As a matter of fact, the more

the nasal bones can be elevated, the more amenable will be the residual deformity to plastic correction.

Treatment of old fractures of the nose. Nasal deformities due to old fractures of the nasal bones and septum can be repaired only by rhinoplastic procedures, a subject which is too broad to be discussed in this paper. However, if the defect involves a residual depression of the nasal bridge, the use of a cartilage or bone graft to build up the nose to normal contour is indicated. I believe that no foreign substances are suitable for this purpose. Fresh autogenous cartilage implants have the disadvantage of warping and becoming distorted (figure 3). Cartilage obtained at necropsy, although it will not warp, has a pronounced tendency to undergo absorption. Because of these undesirable features, I have practically discontinued the use of cartilage for nasal implantation. Instead, I prefer to use cancellous bone from the crest of the ilium (figure 4). A bone graft from which the hard cortex has been removed heals readily, and since it is composed largely of cancellous bone, it can easily be cut to the desired shape by the use of rongeurs and files (figure 5). The bone implant of proper contour is inserted through an incision at the lower border of the nose, the nasal skin having been completely undermined so as to leave a subcutaneous pocket over the nasal bridge for reception of the graft.

If the nasal depression involves only the cartilaginous part of the dorsum, a portion of the bony bridge above should be removed with saws or chisel. This permits the use of a bone implant extending from the nasal tip almost to the glabella (figure 6), thereby producing a better cosmetic effect than would be achieved with a small transplant applied to the lower half of the nose.

I have found it preferable to insert the bone graft through an incision at the lower border of the nose rather than through an incision in the nostril. Retraction of the edges of the former incision provides exposure of the lower lateral cartilages, which can be freed and sutured together to make a normal nasal tip. The bone graft then occupies a position above the tip which produces a nose of pleasing contour (figures 5 and 6).

One of the most difficult traumatic nasal deformities to repair is the nose deflected to one side because of an old injury in which the nasal bones and septum were fractured and displaced in childhood. Many of these severe nasal defects could have been prevented if, at the time of the

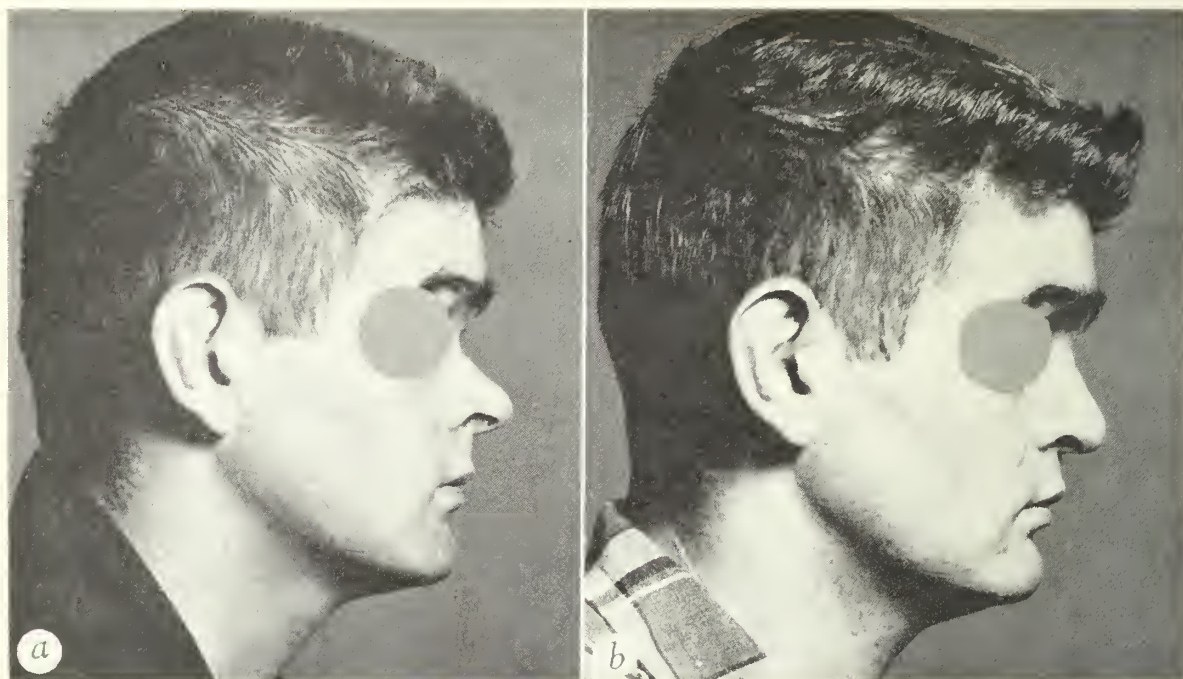


Fig. 5. *a*. Residual depression of nasal bridge due to old crushing injury to nose. *b*. Defect corrected by means of autogenous iliac bone graft inserted through incision at lower border of nose.

original injury, the child had been given general anesthesia to facilitate proper manipulation and immobilization of the bony fragments.

If the deflection is confined to the bony bridge and is not associated with any particular dis-

placement of the nasal septum, the deformity is not difficult to correct. Fracturing the frontal process of each maxilla with a saw or an osteotome permits infracturing of the nasal bones, which can be molded into proper position. Sub-



Fig. 6. *a*. Depression defect of cartilaginous portion of bridge of nose due to old injury. *b*. Deformity corrected by means of autogenous iliac bone graft inserted through incision at lower border of nose. Prominence produced by nasal bones was removed with a chisel so that bone graft could be extended from nasal tip almost to glabella.

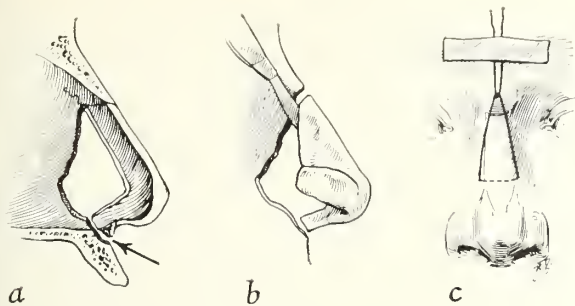


Fig. 7. Kazanjian's method of straightening external nose in defects due to septal deflection. *a*. Submucous resection of cartilaginous part of septum is done, leaving a right-angled segment of septal cartilage intact beneath nasal bridge and above columella. Chisel is used to separate spinous process from maxilla. *b*. Small knife detaches upper lateral cartilages and remnant of septum from lower border of nasal bones. *c*. Lateral cartilages and remnant of septum are immobilized by silk suture passed through cartilaginous part of nose and attached to forehead by adhesive tape.

sequent immobilization of the nasal bones with an external splint and intranasal petroleum jelly packs for a few days will restore the nose to a satisfactory contour.

However, if the irregularity or deflection of the nose is due largely to deflection of the nasal septum, correction of the deformity becomes an extremely difficult problem. In such cases, repair of the nasal deformity requires not only a routine rhinoplasty but also a submucous resection

of the nasal septum. The technic that I have found most satisfactory in the repair of nasal defects caused by combined deflection of the nasal bones and nasal septum is an adaptation (figures 7 and 8) of an operation first described by Kazanjian. It involves an incision in the mucous membrane on one side of the nasal septum about 1 cm. above the columella. This incision is carried down to and through the cartilaginous septum; then, with periosteal elevators, the mucous membrane on each side of the nasal septum is elevated, after which the septal cartilage is completely removed except for a right-angled piece behind the bridge of the nose and above the columella. If badly deflected, the bony portion of the nasal septum can be removed through the same incision. After this type of partial submucous resection of the cartilaginous nasal septum, a routine rhinoplasty is performed to effect whatever changes in nasal contour are required.

As soon as the rhinoplastic part of the operation has been completed, the right-angled segment of the nasal septum below the dorsum of the nose and above the columella is completely separated from the remaining framework of the nose except for its mucosal attachments. Below, a chisel is used to detach the spinous process from the maxilla; this separates the retained segment of septal cartilage from its lower attachment. Above, a small scalpel is used to divide the upper lateral cartilages and remain-



Fig. 8. *a*. Nasal deformity due to old traumatic deflection of nasal bones and septum to left. *b*. Appearance after correction by technic shown in figure 7

ing part of the nasal septum from the lower edge of the nasal bones. This technic permits complete detachment of the upper and lower lateral cartilages and the remnant of nasal septum from the rest of the nose, except for mucosal and dermal attachments, allowing these cartilaginous structures to be placed in any position that appears desirable. They are moved to the midline and are immobilized against the lower edge of the nasal bones by a silk suture passed horizontally through the lower part of the nose and attached to the forehead by adhesive tape. Fur-

ther immobilization is obtained by the use of an external metal splint and intranasal petroleum jelly packs.

In conclusion, I would like to emphasize the fact that regardless of how much time and effort are expended by the surgeon, it is not possible to restore the original contour of every fractured nose. Consequently, one must not expect perfect results in all cases. However, the conscientious care of nasal fractures will hold residual deformities to a minimum, for which the patient will be most appreciative.

IN DOGS WITH HYPOCAPNIA induced by hyperventilation, lactic and pyruvic acids accumulate in the blood, decreasing bicarbonate concentration, to compensate for respiratory alkalosis. Progressive bicarbonate deficit, if extensive, may cause a metabolic acidosis.

Lactic and pyruvic acid values decrease only with lowered $p\text{CO}_2$ concentrations. Hyperventilation, rising pH, or hypoxia do not alter lactic and pyruvic acid values when $p\text{CO}_2$ concentration remain normal. With a normal pH and a lowered $p\text{CO}_2$, lactic and pyruvic acid concentrations rise. Hypocapnia was produced by mechanical hyperventilation in anesthetized dogs. Lactic and pyruvic acid values in arterial blood were determined as the lactate and pyruvate salts. Reduction in $p\text{CO}_2$ produced respiratory alkalosis, which was completely compensated within sixty minutes by a bicarbonate deficit. Increased concentrations of lactic and pyruvic acid accounted for about 74 per cent of the true bicarbonate deficit.

A. EICHENHOLZ, R. O. MULHAUSEN, W. E. ANDERSON, and F. M. MACDONALD: Primary hypocapnia: a cause of metabolic acidosis. *J. Appl. Physiol.* 17:283-288, 1962.

ADMINISTRATION of angiotensin II (Hypertension) and synthetic d-aldosterone effectively reverses endotoxin shock in dogs, the steroid apparently potentiating the pressor agent. *Escherichia coli* endotoxin, 0.55 mg. per kilogram of body weight, was injected into femoral veins of 43 dogs. Shock killed 13 control animals after about twelve hours. Of the remaining endotoxin-treated dogs, 5 of 10 survived after angiotensin II, 2 of 10 after d-aldosterone, and 8 of 10 after combined d-aldosterone-angiotensin II administration. Intravenous dose of d-aldosterone was 0.2 mg.; 1 mg. of angiotensin II in 100 cc. of 5% dextrose and distilled water was slowly infused in amounts necessary to maintain blood pressure at about 100 mm. Hg.—about 0.65 mg. when angiotensin II was used alone and about 0.09 mm. Hg. when combined with steroid.

W. W. SPINK and J. VICK: Canine endotoxin shock: Reversal with aldosterone and angiotensin II (Hypertension) (27255). *Proc. Soc. Exper. Biol. & Med.* 109:521-522, 1962.

Brucellosis on a Ranch

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Bismarck, North Dakota

IT HAS BEEN DEMONSTRATED before that human brucellosis has no unique symptoms and occurs erratically in a community exposed to it.¹ The following presentation, however, illustrates this exceptionally well, since the community involved consisted of 4 families who were relatively isolated on a ranch and had one common source of infection. Thus the characteristics of brucellosis epidemiology are shown—for every case recognized clinically, one should find asymptomatic cases.²

The following case led to the discovery of brucellosis in this community and illustrates that brucellosis must be suspected to be diagnosed.

L. L., age 51, is a housewife who came to the clinic with a complaint of anorexia and fever of about 102° F. for one week. No cardiorespiratory, gastrointestinal, or genitourinary symptoms were admitted. She had recently received penicillin elsewhere for a chronic kidney infection and noted some subjective improvement. Examination showed a temperature of 100° F. orally, blood pressure 116/60, pulse 110 and regular, and no abnormal physical findings except a questionable tenderness over the left kidney. Laboratory data revealed hemoglobin, 74 per cent; white blood count, 5,800; urine, specific gravity 1.014, albumen 0, sugar 0, and an occasional leukocyte. The patient was hospitalized.

Chest roentgenograms; kidney, ureter, and bladder films; intravenous pyelogram; and electrocardiograms were normal. Blood urea was 30 mg. per cent, and Kahn, Mazzini, and Paul-Bunnell tests were all negative. Sedimentation rate was 44 mm. in one hour. A catheterized urine specimen was cultured and grew a colony of Gram-positive cocci sensitive to oxytetracycline. Antibody tests for typhoid O and H and paratyphoid A and B and *Proteus* OX19 were all negative but were positive through 1:320 dilution for *Brucella abortus*.

The patient was placed on therapy of oxytetracycline for four days, which was changed to dihydrostreptomycin and sulfadiazine with sodium bicarbonate because of the antibody report; she continued on this until her discharge from the hospital twelve days after admission. Her temperature became normal on the fourth hospital day and she felt quite well after that. A blood culture was obtained before starting this antibiotic therapy; when it was later reported as negative it was learned that through error a culture was not grown under CO₂ specifically for *Brucella*. (Accordingly, only a presumptive diagnosis of brucellosis may be made on her clinical infection.)

A month after hospitalization she had no complaints and showed a normal physical examination but had a sedimentation rate of 35 mm. in one hour. Her *Brucella abortus* antibody titer then was 1:640.

Because of the positive titer of *Brucella abortus* antibody, she was questioned concerning possible exposure to brucellosis. It was found that for a long time she had been drinking raw milk obtained from a herd of cows used for a private milk supply on the ranch where she lived.

All the members of 4 families living and working on the ranch had been using this milk supply. They were all contacted, and a blood specimen was obtained from each person for antibody titer. The results are shown in the table. Study of the table agrees with previous findings³ that it is unusual to have more than one individual in a family manifest evidence of brucellosis, although all members may be exposed equally to the infection.

Of the 21 people living on the ranch and using the common milk supply, 6 showed a positive titer of antibodies to *Brucella abortus*. One was the patient L. L., whose case report was given previously. The other 5 were questioned and examined. It is presumed these 5 persons acquired the disease recently, since the herds had always been Bang's negative and had been tested several months earlier and no positive reactors to Bang's disease had been found. All

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TABLE
RESULTS OF TESTS FOR ANTIBODY TITER

Case	Relation to patient	Age	Sex	<i>Brucella abortus</i> antibody titer
1. L. L.	Self	51	F	1:320
2. A. L.	Husband	61	M	0
3. O. L.	Daughter	15	F	0
4. R. L.	Son	13	M	1:80 (weak 1:160)
5. J. L.	Mother-in-law	84	F	0
6. N. H.	Brother	49	M	0
7. M. H.	Sister-in-law	33	F	0
8. W. H.	Nephew	9	M	0
9. J. H.	Nephew	6	M	0
10. C. H.	Niece	4	F	1:160 (weak 1:320)
11. D. H.	Nephew	3	M	0
12. A. H.	Niece	3	F	0
13. P. D.	None	41	M	0
14. T. D.	None	33	F	0
15. L. D.	None	17	M	1:320
16. M. D.	None	14	M	1:320
17. W. D.	None	11	M	0
18. G. D.	None	7	F	0
19. V. D.	None	4	M	0
20. J. F.	None	26	M	1:640
21. T. F.	None	27	M	0

these people were asymptomatic, in good health, and showed no evidence of disease on physical examination, except J. F. (case 20). This man admitted some mild tiredness for the last two weeks before his clinic visit. Physical examination was normal; sedimentation rate was 11 mm. in one hour. He stated he did the butchering for the ranch and thus handled raw meat, in addition to drinking the milk.

It is interesting to note that 4 of the 6 people with *Brucella* antibodies were males, which agrees with the preponderance of males found before.³

Investigation of the herd showed 1 milch cow of the dairy herd and 27 of the beef herd to have positive tests for Bang's disease. These infected cattle were eliminated from the ranch. On our advice a household pasteurizer was obtained for pasteurizing all the milk consumed.

Because of the possibility of developing a chronic infection³ the 5 persons with *Brucella* antibodies other than the case described were given a course of chlortetracycline therapy. All completed the course without incidence of side reactions from the drug.

SUMMARY

A recent case of brucellosis is described and its source traced. The spread of the disease is shown in a small, isolated, ranch community. While 21 people were exposed to an approximately equal degree, only 6 were found to have had the disease, as demonstrated by development of *Brucella abortus* antibodies. Of these 6, definite symptoms developed in only 1 patient.

CONCLUSIONS

When a group of people have been exposed to a source of brucellosis, only a fraction of them will acquire the disease. Of this fraction symptoms may develop in a much smaller number.

When the practitioner diagnoses a case of brucellosis, he must not only investigate the source of infection but also trace its spread to all other potential victims.

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Lung Tumors

Clinical, Roentgenologic, and Pathologic Observations

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BEFORE chest exploration for lung tumors, there should be confirmatory findings in the clinical studies performed. The studies may consist of bronchoscopic aspiration of secretion and isolation of tumor cells, tissue biopsy, scalene lymph node dissection, and cervical or mediastinal biopsy examination. In a large proportion of cases, however, examination by these methods is noncontributory in establishing a diagnosis of tumor. In consequence, a long interval may prevail between the patient's first examination and the time of thoracotomy. The investigation herein reported is concerned with analysis of symptoms, roentgenologic observations, and histologic data in a group of surgically proved tumors.

Symptoms were correlated with roentgenographic abnormality, and histopathology was considered in relationship to peculiarity in either clinical symptoms or roentgenologic manifestations. Other phases studied were the incidence of calcification within the tumor site; simulation of other pathologic conditions; and occurrence of metastatic lesions from other sites, as well as dissemination from the lungs to other organs. Tumor detection yield was sought among patients who had routine x-ray examination; an appraisal was made of the frequency with which a diagnosis of tumor could be entertained when radiographs were viewed in retrospect. In addition, the nature of symptoms was assessed with respect to the operability of the lesion and to the extent that the index of suspicion of tumor is evident in a thoracic clinic.

MATERIALS AND METHODS

Reported here are 50 cases which came to the attention of the author because of radiographic findings when a clinical examination was implemented by chest radiography or when an abnormality was noted on routine x-ray examination. The diagnosis was established in 39 cases in the Veterans Administration Hospital and in 11 cases

in public hospitals, which the patients entered through their own choice of private surgeon. It was possible to review the clinical, roentgenologic, and pathologic protocols of the latter group.

Bronchoscopic examination. Bronchoscopy was performed in 33 patients, with the following positive findings: in 7, biopsy evidence of neoplasia; in 1, carcinoma cells in the bronchial washing; in 4, indirect evidence of tumor, noted in the form of external pressure upon the bronchus observed in its lumen and subsequently confirmed at the time of exploration; and in 6, macroscopic evidence of tumor in the main stem or segmental bronchial lumen not accessible to biopsy but verified by thoracotomy. Thus, of 33 cases in which this method of examination was performed, positive diagnostic information was received in 18, while examination was noncontributory in 15.

Scalene lymph node dissection. This procedure is usually reserved for the following instances: (1) when carcinoma is suspected but bronchoscopic and cytologic examinations are negative; (2) when tuberculosis is suspected but bacteriologic study is negative; and (3) when lymphosarcoma or collagen granuloma is suspected.¹ Scalene lymph node dissection was performed in 11 cases; 4 were positive and 7 were negative for tumor.

Interval between clinical examination and exploration. This period has been categorized into units of weeks, months, and years. In 19 cases, the interval was one to four weeks; in another 19 cases, the interval was one to eleven months; and in the remaining 12 cases, the interval was one to three years—one year in 4 cases, two years in 3 cases, and three years in 5 cases.

History of symptoms. The cases were designated as asymptomatic, acute, recent, and chronic. On routine x-ray examination, 8 cases were asymptomatic; 16 were recent (7 acute, with symptoms lasting days or weeks, and 9 recent, with symptoms lasting several months); and 26 were chronic (symptoms present a year or longer). A patient in the latter group is not

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Fig. 1. Routine roentgenogram on separation from service. Note round density at left base. Patient was asymptomatic. Resection revealed hamartoma (1951).

apt to seek medical attention. The asymptomatic cases showed a wide variety of pathologic entities—1 carcinoma, 2 thymomas, 1 hamartoma, 1 neurofibroma, 1 ganglioneuroma, 1 hemangioendothelioma, and 1 lymphosarcoma of the mediastinal nodes (figure 1). (In describing Hodgkin's pathology in the mediastinal lymph nodes, the term lymphosarcoma is here used interchangeably.)

OBSERVATIONS

Histopathology and corresponding x-ray abnormality. Tumor classification, with accompanying x-ray manifestations in each category, as seen in this group is described in table 1. Roentgenologic findings were as follows (see figures 2 to 5):

- Of the bronchogenic carcinomas, 1 appeared as a nondescript infiltrate; 4, as hilar tumors; 5, as parenchymal tumors; 6, as pneumonitis; 2, as mediastinal tumors; 5, as lobar atelectasis; 4, as granulomas; 1, as uniform apical density, or Pancoast's tumor; and 2, as nondescript parenchymal infiltrates.
- Of the 3 thymomas, 1 was benign and appeared as a cyst and 2 were malignant and ap-

TABLE 1
ROENTGENOLOGIC FINDINGS IN THE TUMOR
GROUP HEREIN REPORTED

Tumor	No. cases	Roentgenologic abnormality
Carcinoma, bronchogenic	1	Nondescript infiltrate
Carcinoma, bronchogenic	2	Hilar tumor Parenchymal tumor
Thymoma	3	Cystlike abnormality Mediastinal tumor Parenchymal tumor
Adenocarcinoma	4	Unilateral pleural effusion*
Carcinoma, bronchogenic	3	Hilar tumor*
Carcinoma, bronchogenic	6	Pneumonitis*
Carcinoma, bronchogenic	2	Mediastinal tumor*
Carcinoma, bronchogenic	5	Lobar atelectasis*
Carcinoma, bronchogenic	4	Granuloma*
Lymphosarcoma	3	Bilateral hilar adenopathy (2 cases) Unilateral hilar adenopathy (1 case)
Carcinoma, bronchogenic	1	Uniform apical density (Pancoast's tumor)
Carcinoma, bronchogenic	1	Nondescript parenchymal infiltrate
Carcinoma, bronchogenic	4	Parenchymal tumor*
Carcinoma, bronchogenic	1	Nondescript parenchymal infiltrate
Benign papilloma of bronchus	1	Lobular atelectasis
Neurofibroma	2	Vertebral body tumor Lung cyst
Hemangioendothelioma	1	Parenchymal tumor
Ganglioneuroma	1	Mediastinal tumor
Bronchial adenoma	5	Unilateral hilar adenopathy Unilateral bronchopneumonia Lobar atelectasis Pneumonitis Massive hemithoracic density

*All cases

peared as mediastinal and parenchymal tumors, respectively.

- Of the 4 adenocarcinomas, 1 appeared as an effusion; 1, as pneumonitis; 1, as a granuloma; and 1, as an atelectatic lobe.

- Of the 3 lymphosarcomas, 2 appeared as bilateral hilar adenopathy and 1, as unilateral adenopathy.

- Of the 2 neurofibromas, 1 appeared as a vertebral body tumor and 1, as a lung cyst.

- Of the 5 bronchial adenomas, 1 appeared as unilateral hilar adenopathy; 1, as unilateral bronchopneumonia; 1, as lobar atelectasis; 1, as

TABLE 2
HISTOLOGIC CHARACTER OF TUMORS

Benign (12)		Malignant (38)	
Mild	Severe	Mild	Severe
10	2	23	15

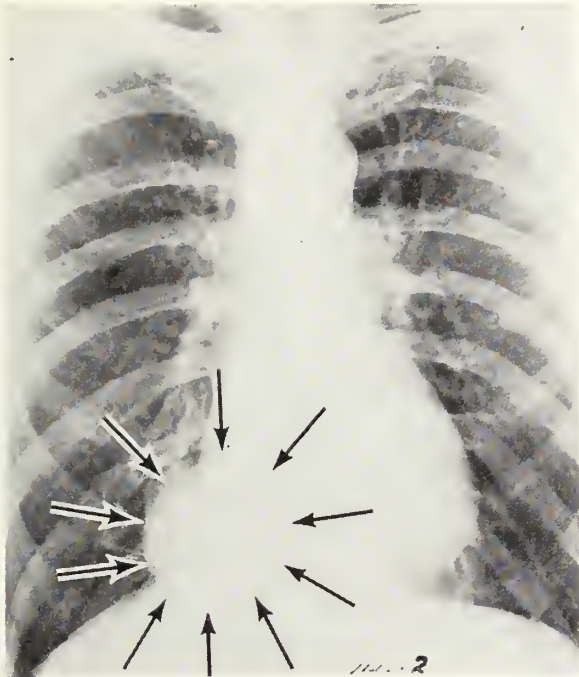


Fig. 2. Cystlike abnormality was found to be a neurofibroma.

pneumonitis; and 1, as a massive hemithoracic density.

- The benign papilloma of the bronchus appeared as a zone of lobular atelectasis; the hemangioendothelioma, as a parenchymal tumor; and the ganglioneuroma, as a mediastinal tumor.

Histopathology of tumors and corresponding severity of symptoms. Table 2 describes the correlation between nature of the tumor and severity of symptoms. The incidence of severe symptoms is low among benign tumors and relatively high among malignant tumors. However, the high incidence of mild symptoms in the malignant group of cases is surprising. Mild symptomatology could readily mislead physicians of limited experience in tumor diagnosis.

Calcification within tumors. According to the radiographs, 1 hamartoma and 1 adenocarcinoma had calcification.

Simulation of other conditions. Radiographically, tumors can be mistaken for other diseases. An infiltrate caused by a highly malignant carcinoma can look like an innocent condition; thus, one malignant carcinoma looked like a nondescript infiltrate and another, a typical, mild, tuberculous infiltrate. The first case was

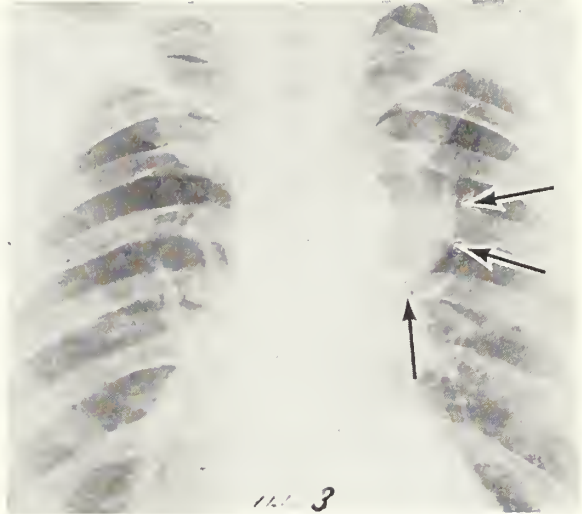


Fig. 3. Paramediastinal density (left), resembling cyst, was found to be a thymoma.

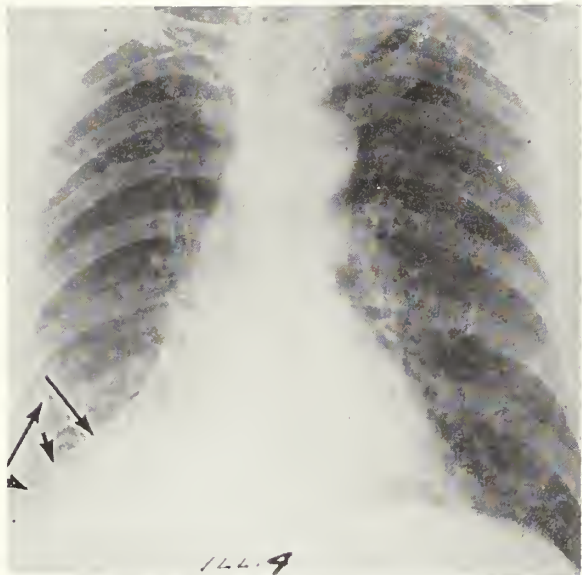


Fig. 4. Bronchogenic carcinoma masqueraded as pneumonitis. Note typical bronchopneumonic infiltration (arrows).

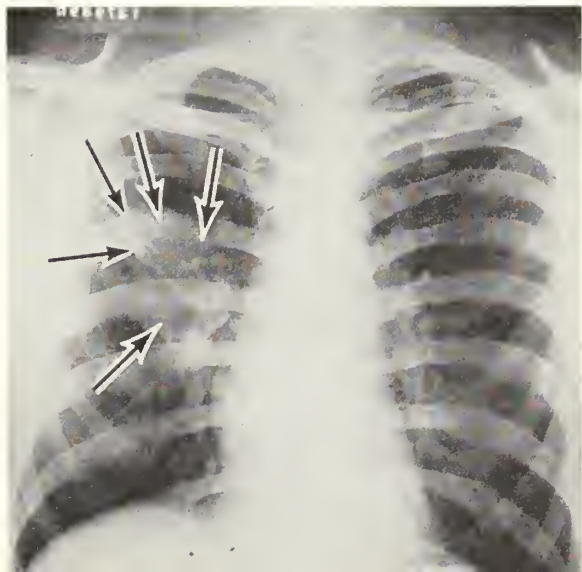


Fig. 5. Recurring pneumonitis and episodes of hemoptysis (arrows), considered to be caused by bronchopulmonary suppurative disease, were found to be caused by an adenoma of the bronchus. Lobectomy was performed.

inoperable because the lung could not be mobilized. The second case did not respond to tuberculostatic drugs, and a pneumonectomy was performed.

In 2 cases, a mature thymoma and a neurofibroma, routine films taken one year earlier showed an abnormality that looked like a cyst. In a group of 8 cases, consisting of 6 bronchogenic carcinomas and 2 bronchial adenomas, roentgenograms showed pneumonitis. One of these was considered a suppurative type of pneumonitis; thoracic exploration showed it to be a bronchial adenoma that induced airway block, with ensuing infection.

Additional examples of tumors simulating other conditions are:

1. A bronchial carcinoma complicated by an effusion was considered tuberculous on hospital admission because the fluid showed lymphocytosis.

2. One carcinoma showed up as a nonspecific granulomatous process, and diagnoses of tuberculosis and tumor were entertained; thoracotomy proved the former diagnosis in error.

3. One adenocarcinoma looked like a tuberculous infiltrate.

4. One carcinoma of the bronchus resembled a typical tuberculous process.

5. One bronchial carcinoma simulated indolent tuberculosis.

6. One patient with carcinoma, originally diagnosed as having tuberculosis, was treated with tuberculostatic drugs without clinical or radiologic response; the correct diagnosis was established by thoracotomy.

7. Lastly, a case of neurofibroma masqueraded for years as a vertebral tumor.

Several illustrative cases are presented in table 3, with the pathologic findings after thoracotomy (figures 6 to 8).

Incidence of metastatic phenomena. Metastasis, either from distant sites to the lung or from the lung to neighboring or distant structures, was noted in the following instances (table 4). One adenocarcinoma was observed that had been preceded by a testicular tumor of identical histopathology removed eighteen years previously. One carcinoma was found a year after the finding of a similar neoplasm in the glossopharyngeal region. One lymphosarcoma was found sixteen years after finding identical histopathology in the glands of an axilla. Two carcinomas and 1 adenocarcinoma were considered metastatic tumors, but the primary site was not identified. One malignant thymoma metastasized to the mediastinal lymph nodes. One broncho-

TABLE 3
LUNG TUMORS SIMULATING OTHER CONDITIONS

Case	Clinical consideration	Findings at operation
1	Nondescript infiltrate	Bronchogenic carcinoma, inoperable
2	Pneumonitis	Bronchogenic carcinoma
3	Tuberculous granuloma	Bronchogenic carcinoma
4	Cyst	Neurofibroma
5	Tuberculosis	Bronchogenic carcinoma
6	Cyst	Thymoma
7	Vertebral tumor	Neurofibroma
8	Tuberculosis	Bronchogenic carcinoma
9	Tuberculosis	Adenocarcinoma
10	Tuberculoma	Hamartoma

genic carcinoma metastasized to the trachea and mediastinal lymph nodes; one, to the pancreas, and one, to the body of D₁₂. One adenocarcinoma metastasized to the mediastinal lymph nodes, and a Pancoast tumor, to D₆.

Severity of symptoms and operability. In the relatively small series of cases with which this paper deals, an analysis of the relationship between symptom severity and operability can elicit only a trend when statistically considered. Table 5 shows an interesting relationship. In viewing the figures, we note a good numerical parity between cases with mild symptoms (23) and cases with severe symptoms (25). In the mild-symptom group, there are only 4 inoperable cases, as compared with 16 cases that are inoperable in the severe-symptom group. As a corollary, there were 19 operable cases in the mild-symptom group and only 9 in the severe-symptom group.

TABLE 4
EXAMPLES OF METASTASIS

Lung tumor	Direction of metastasis
Metastatic	
adenocarcinoma	from testicle*
carcinoma	from glossopharyngeal region†
lymphosarcoma	from glands of axilla‡
carcinoma	primary site unknown
carcinoma	primary site unknown
adenocarcinoma	primary site unknown
Primary	
malignant thymoma	to mediastinal lymph nodes
bronchogenic carcinoma	to trachea and mediastinal lymph nodes
bronchogenic carcinoma	to pancreas
bronchogenic carcinoma	to body of D ₁₂
adenocarcinoma	to mediastinal lymph nodes
Pancoast's tumor (right upper lobe)	to D ₆

*Similar tumor had been removed from testicle 18 years previously.

†Similar tumor had been removed from glossopharyngeal region 1 year previously.

‡Glands of similar histopathologic structure had been removed from axilla 16 years previously.

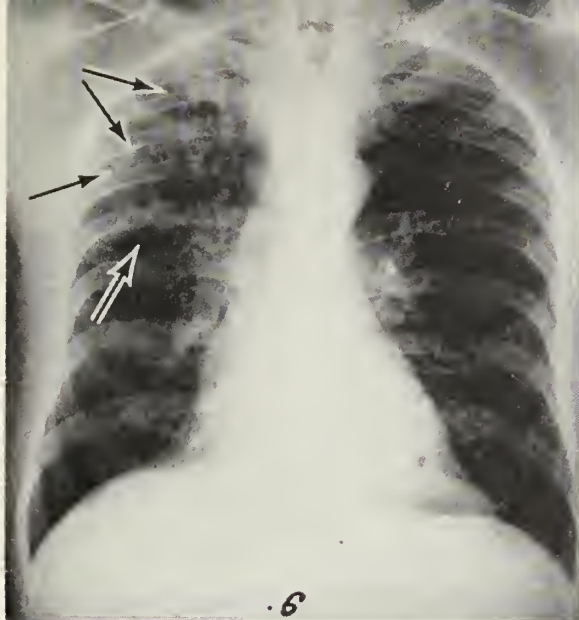


Fig. 6. Acute pneumonitis in right upper lobe region. Illness began several days before film was made (February 19, 1957).

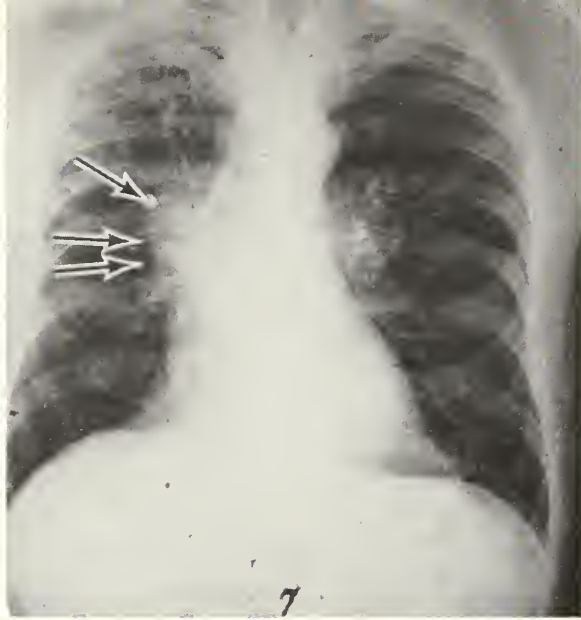
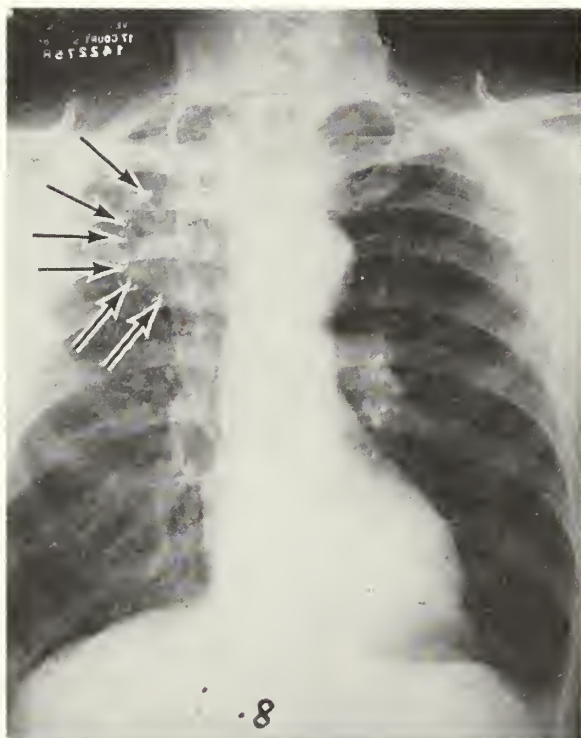


Fig. 7. Roentgenogram, made March 16, 1957, of patient referred to in figure 6. Note enlargement of right hilus. Patient did not respond to antibiotics or antituberculosis drugs. On exploration, carcinoma was found. Patient died six weeks later.

Fig. 8. Infiltration in upper lobe. Note clear outer zone. Tuberculosis was considered, but exploration showed carcinoma in right upper lobe.



Retrospective considerations. The experienced clinician sometimes obtains the impression, after a review of a series of x-ray films in a given case, that, retrospectively, an abnormality could have been considered at some time prior to the evaluation of current films. It should be stressed, however, that the common deterrent to a consideration of anomalous shadows of a borderline nature is either absence of symptoms or a history of chronic respiratory disease symptomatology, in which instance slight deviation from normal could be overlooked. Especially is it easy to miss a case of tuberculosis when the condition appears in an unusual anatomic site. It must be said that neoplasia can be so masked by other abnormalities that it could easily be missed. The only hope is that it is not missed too often. Certainly, as the physician interprets the films, he must be ever on the alert to recognize deviations from the norm. Of course, when he notes changes which he qualifies by the phrase "within normal limits," he assigns to himself a very difficult task in x-ray interpretation.

Fig. 9. Mediastinal adenopathy was metastatic from Hodgkin's paraneoplasia of axilla, treated sixteen years previously.

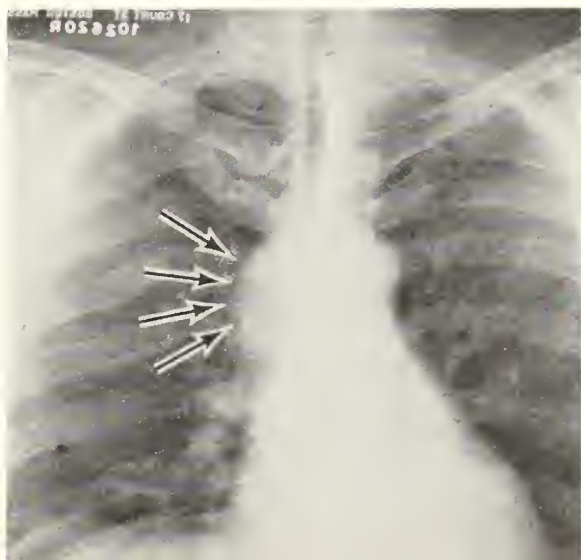


TABLE 5
SYMPTOMATOLOGY vs. OPERABILITY*

Mild symptoms (23 cases)		Severe symptoms (25 cases)	
Operable	Inoperable	Operable	Inoperable
19	4	9	16

*2 cases of lymphosarcoma received x-ray treatment

Although, in this study, there were a number of instances in which tumors resembled other conditions, an analysis of the 50 cases studied reveals only 5 instances in which we could have done better in diagnosis, retrospectively considered. Table 6 indicates the mechanisms involved.

DISCUSSION

In the past, activities in a pulmonary clinic were concerned with tuberculosis, bronchopulmonary infections, pneumoconiosis, sarcoidosis, berylliosis, collagen disease, mycotic infections, emphysema, and cystic disease. In recent years, the most startling response to chest abnormality has been evoked by the relatively frequent finding of lung tumors. Currently, the chest physician is experiencing a dynamic awareness that he has to maintain at all times a high index of suspicion of the possible presence of neoplasia so he may be better able to contribute to earlier diagnosis and treatment.

Bougout and associates² stress that, in the absence of cancerocidal agents for use alone or combined with surgery, early tumor detection is the key to early cure. Overholt and associates³ emphasize that serious neoplasia may be present in the absence of symptoms. In one series observed by the latter group, there were 46 silent neoplasms among 268 cases of tumor explored—an incidence of 16 per cent. They state further that lesions without, rather than lesions with, symptoms are more apt to be carcinomas. Moreover, they do not favor a waiting period of six to eight weeks for the acid-fast bacilli culture study

TABLE 6
RETROSPECTIVE CONSIDERATIONS

X-ray abnormality	Initial diagnosis	Tissue diagnosis
Infiltrate in inner zone of right upper lobe	Tuberculosis	Carcinoma
Infiltrate throughout entire right upper lobe	Pneumonia; tuberculosis	Carcinoma
Persistent enlargement of hilar lymph node in addition to upper lobe infiltration	Nonspecific residual of pneumonia	Adenoma of bronchus
Nondescript infiltrate in right upper lobe of three years' duration	Innocuous infiltrate	Adenocarcinoma
Hilar shadow of ten years' duration	Innocuous lymph node	Ganglioneuroma

of bronchial secretions when the roentgenogram shows a nondescript infiltrate. They prefer an exploratory thoracotomy. Wilkins⁴ described a group of 77 patients studied at the Massachusetts General Hospital, none of whom had respiratory symptoms; all were diagnosed upon exploration as having malignant tumors. In the series of cases herein reported, there were 8 silent tumors, of which 1 was a coin lesion.

Bronchoscopic examination. Bronchoscopy was fruitful in a little over one-half of the cases in which it was performed—18 out of 33 cases. When a breakdown of this procedure was made, we noted that more cases showed indirect evidence of tumor than was found on direct bronchoscopic biopsy. This experience is illuminating and emphasizes the importance of the services of an experienced bronchoscopist who is proficient in detecting anatomic variations in the bronchial lumen pattern. In this series, intraluminal evidence of extrinsic pressure effects was found in 4 patients and microscopic evidence of a tumor which did not yield biopsy material was found in 6. The latter finding gave the clue to the bronchoscopist that a tumor was present, and this was confirmed by subsequent thoracotomy. Benedict⁵ reports positive findings in 189 of 309 cases of bronchogenic carcinoma—an incidence of 61 per cent. In the group herein reported, only 1 case yielded cytologic evidence of tumor in the bronchial lavage fluid.

Scalene lymph node dissection. When scalene lymph node dissection was used for tumor diagnosis, findings were positive in 4 of 11 cases, an incidence of 36 per cent. Umiker⁶ takes a dim view of the efficacy of this method. In observing 100 cases of bronchogenic carcinoma, he found 22 positive cases out of 78 cases in which lymph node dissection was performed and considers this procedure the least sensitive diagnostic modality. He claims that more carcinoma is detected by the cytologic method than by bronchoscopy and scalene node dissection combined.

Examination-exploration interval. In this series of cases, the interval between clinical examination and thoracotomy was one to four weeks in 19 cases, which can be considered a reasonable period. In another 19 cases, the interval was one to eleven months, which indicates a lag in the approach to the tumor problem. In the remaining 12 cases, the interval was one to three years. It should be stated that procrastination is understandable insofar as the patient is concerned. However, if the physician postpones exploration despite adequate indications, he can miss an opportunity for early excision of the tumor. In this regard, Overholt and associates³

make the following point: "Serial x-ray examination of the chest to demonstrate possible change in the size of the shadow is most undependable, wastes time and may sacrifice a life." They decry the phrase, which appears in x-ray laboratory reports, "advise repeat x-ray in 1 to 3 months." Under these circumstances, it is understandable that the patient, in his desire to evade the issue, is apt to postpone the x-ray reexamination.

Symptoms. The history of symptoms in neoplasia is intriguing. The most dramatic cases are the silent tumors. These are found usually during a routine x-ray examination. They startle us if they turn out to be carcinomas. In a group of such silent tumors reported by Pate and associates,⁷ the patients were treated for various diseases. Of 42 patients with what proved to be carcinoma, 16 had joint, 13 had neurologic, and 11 had gastrointestinal symptoms; in only 2 cases was there reference to the respiratory system—not at all suspicious for neoplasia. In the series of cases herein presented, 8 were silent tumors.

Roentgenology. Regarding histopathology and corresponding x-ray abnormality, it should be stressed that the diagnosis of tumors cannot be made from films alone. Neoplasms are notorious masqueraders of other chest diseases. Moreover, as shown by Roswit and Unger,⁸ lesions which may not be seen on conventional roentgenograms—for example, those in "dark areas" in the thorax, such as the thoracic inlet, upper mediastinum, hilus, and diaphragm regions—can be detected by transverse (third dimension) tomography. In the series of cases herein reported, the following histopathology and corresponding x-ray relationships were noted: (1) an alveolar-cell carcinoma and undifferentiated carcinoma appeared as a nondescript, innocent-looking density, whereas a thymoma appeared as a benign cyst; (2) of 4 adenocarcinomas, 1 appeared as an effusion; 1, as a lobar atelectasis; 1, as a granuloma; and 1, as pneumonitis; (3) 6 carcinomas appeared as pneumonitis; (4) 4 bronchogenic carcinomas appeared as granulomas; (5) 1 undifferentiated carcinoma appeared as a nondescript parenchymal infiltrate; and (6) 2 neurofibromas appeared as a vertebral body tumor and lung cyst, respectively.

Differential diagnosis. In a discussion of basic principles upon which a diagnosis is considered, certain anomalies are notorious. Thus, although atelectasis should be looked upon as the sequela of bronchial lumen obstruction from within or as resulting from extraluminal pressure, the most common diagnoses made under these circumstances are bronchopneumonia or virus pneumonia. Again, in a consideration of tumors confined

to the mediastinum, the report by Nelson and associates⁹ is significant: one-half of 114 cases were asymptomatic.

In the series of tumors reported here, 35 were carcinomas or adenocarcinomas. Some authors^{10,11} classify these neoplasms in terms of dominant cell structure, that is, as squamous cell, large cell, oat-cell, and alveolar cell carcinomas. Wilkins and Sweet¹⁰ consider the large cell and oat-cell the most malignant of all bronchogenic carcinomas. They also stress the importance of more frequent screening of the population to make the search for tumors more effective.

The relationship between the benign or malignant nature of tumors vis-à-vis mildness or severity of symptoms is of considerable interest. Among the benign tumors in this group, symptoms of a severe nature were uncommon. Conversely, severe symptoms were found in more than half of the malignant cases.

Tumor calcification was observed in only 2 cases. In this connection, Roswit and Unger⁸ stress that, in interpreting roentgenograms, one should be on guard against calling artifact flecks of calcium.

In regard to tumors simulating other conditions, it was noted that serious neoplasia can be mistaken roentgenologically for innocent-looking infiltration—the so-called nondescript density in the parenchyma. Further examples can be enumerated, such as:

- A solid tumor, benign or malignant, could resemble a simple cyst; in this series, 1 thymoma and 1 neurofibroma resembled a cyst.
- Carcinoma can manifest itself as pneumonitis; this was noted in 8 cases. From a diagnostic point of view, this can be a dangerous masquerade, as treatment with antibiotics is apt to clear the process, commonly the result of inadequate bronchial drainage in a lobar segment, and can readily give the physician a false sense of security clinically.
- When an infiltrate involves the upper lobe, it can be mistaken for tuberculosis. In the series reported in this paper, there were 6 such cases. Of course, a therapeutic test with tuberculostatic drugs can be tried. If no effects are noted, it could be presumed that tuberculosis is not the cause of the condition.
- The occurrence of an effusion with lymphocytosis is always a problem in differential diagnosis, since it could be caused by tuberculosis as well as by a tumor.
- A neurofibroma may masquerade for years as a vertebral body tumor, as happened in 1 of these cases.

Metastasis. Metastatic lesions tend to be pe-

ripherally located; hence it is more difficult to recover tumor cells on bronchial washing or sputum study than in cases in which the bronchus is invaded. In the experience of Rosenberg and associates,¹² bronchial invasion occurred as metastasis in 20 of 50 cases. They state that "this low prevalence of bronchial invasion in addition to the tendency for metastatic lesions to be peripheral are factors hindering the recovery of malignant cells in sputum or bronchial washings."¹² In the series reported here, 2 cases are striking: an adenocarcinoma of the lung found eighteen years after removal of a histologically identical tumor from the testicle and lymph node neoplasia in the mediastinum found sixteen years after isolation and treatment of a similar condition, diagnosed as Hodgkin's disease, in the axilla.

SUMMARY

1. Irregular infiltration in the upper lobe region may not be caused by tuberculosis. Especially should the clinician be on guard when the medial portion of the lobe is involved. In the latter instance, the infiltrate is usually not due to tuberculosis and may be due to carcinoma.

2. When initial examination and roentgenologic study suggest a tumor, it is more realistic to perform an early thoracotomy than to consign the patient to observation.

3. The suspicion of neoplasia should be entertained in the presence of atelectasis, delayed resolution of pneumonitis, and suspected tuberculosis when there is no response to tuberculo-static drugs.

4. Neoplasia may be present in the absence of symptoms, and many tumors are found only because of routine x-ray films. Lastly, the index of suspicion of tumor must be maintained at a high level if the physician is to contribute to early diagnosis and treatment of lung tumors.

The author wishes to thank Mr. Shaffer, former chief, and Mr. Milne, present chief, of the photographic laboratory, Veterans Administration Hospital, for reproducing the original roentgenograms and to thank the surgeons who made available the clinical, roentgenologic, and pathologic protocols of the 11 private patients used in this study.

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The Correlations of Dermatology and Cardiology

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THE PAYMENT OF homage and honor to a former teacher, a professor of medicine, a cardiologist, and a great man naturally leads me to a consideration of mutual interests in both our fields of medicine. Thus, I have chosen for my topic a gathering of facts, thoughts, and philosophies pertaining to both cardiology and to dermatology, for George Fahr's lessons in physical diagnosis first stimulated my interest in cutaneous medicine. He, more than others, realized that the skin reflects signs of underlying disease, and he first taught many young fledglings in medicine of its importance.

In this recounting of similar interests, there will be much that is old, little that is new; yet the review should point up the fact that cardiology and dermatology are not widely separated and that each field has knowledge and information advantageous to the other. This review is not complete; a monograph or even a large volume could result from the following correlations.

It has been necessary to categorize arbitrarily the information I wish to emphasize. Let me first then mention a few of the many metabolic or hormonal faults of interest to us both; follow with a brief mention of syphilis and other infections; cite examples of the collagen diseases, the neurocutaneous syndromes, and the congenital defects; and, finally, call attention to some miscellaneous conditions.

METABOLIC AND HORMONAL DEFECTS

The cutaneous signs of hyperthyroidism are usually less apparent to the examining physician than other manifestations, yet the skin is moist, supple, and soft. Also, there may be an unusual type of onycholysis, a serrated separation of the distal edge of the nail from its bed. As opposed to this, in myxedema the skin is dry and scaly, the features are puffy, and the hair is sparse. A

peculiar, localized pretibial myxedema is seen too in patients who have had or still have hyperthyroidism with exophthalmos—this is due to a disturbance of the thyroid-pituitary hormonal balance. I need not recount to you the cardiac implications of myxedema and hyperthyroidism. The myxedema heart was and, I'm sure, still is a favorite of Doctor Fahr's.

As dermatologists, we recognize a number of types of xanthomatosis, including xanthelasma and xanthoma tuberosum, and we can gain a strong suspicion of present or impending atheromatosis by inspection of the skin. These are the xanthomatoses associated with hypercholesterolemia and hyperlipemia. Recently, a patient of ours, only 8 years old, died of coronary sclerosis with essential hypercholesterolemic xanthomatosis.

The syndrome of the functioning carcinoid, elucidated only within the past ten years, is manifested in 4 organ systems: the skin, right side of the heart, lungs, and gastrointestinal tract. The cutaneous manifestation is that of transient flushing, which may persist for as long as thirty minutes but usually lasts for five or ten. Characteristically, the flush appears first in the face and extends caudad. It appears irregularly or even many times daily. It is a blotchy erythema and, when reaching its highest intensity, tends to become cyanotic centrally. The cyanosis clears, and then the flush clears peripherally. These episodes may be precipitated by physical exertion, even by normal bowel movements, by palpation of the abdomen, by proctoscopic procedures, and, in short, by anything that stimulates secretion of 5-hydroxytryptamine from the carcinoid that is functioning (not all carcinoid tumors are functioning). The pathogenesis of the involvement of the right side of the heart in this disease has not been explained as yet. The valves may have become thickened and sclerotic, with the fibrotic sclerosis extending even into the right atrium and pulmonary artery. The ultimate result is tricuspid regurgitation and pulmonary valvular stenosis, which lead to decompensation. Peculiarly, the left side of the heart may be involved

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but only in the presence of a patent foramen ovale. Then the mitral and aortic valves may be affected.

Amyloidosis of the primary systematized type involves the skin and heart among other organs and is associated usually with plasma cell myeloma. There are still other metabolic faults of mutual interest; among these are vitamin deficiency states, including the beriberi of interest to cardiologists and dermatologists, but time does not permit further delving.

SYPHILIS AND OTHER INFECTIOUS DISEASES

By tradition and by training, practice, and experience, dermatologists are syphilologists, and, as such, they not infrequently are called upon to treat patients with syphilitic cardiac and aortic disease. It is known that various structures of the heart and base of the aorta will be involved eventually in approximately 12 per cent of all patients with untreated acquired syphilis. It also is known that in infants, children, and even adults, clinical cardiac involvement by prenatal syphilis is unknown. I say "clinical" because postmortem findings reveal the cardiac structures may be teeming with treponemas. What an interesting paradox and what is the explanation? Incidentally, the so-called therapeutic paradox in relation to syphilitic heart disease is a thing of the past, a misconception, and a disproved theory. May I point out, too, that, in recent years, there has been a steady increase in the incidence of acquired syphilis.

Rheumatic fever and subacute bacterial endocarditis are, of course, of prime interest to the internist and cardiologist. However, I will wager that each of you here today uses the objective cutaneous signs presented by the patient as an aid in diagnosis and, in rheumatic fever, as a determining factor in assessing the course and progress of the disease and as a guide to therapy!

I should point out that, while in the Army and stationed in New Guinea during World War II, a patient died, and, at necropsy, diphtheritic myocarditis was discovered. The source was traced to diphtheritic involvement of the skin. Subsequently, we were able to prove diphtheria of the skin in many soldiers with so-called jungle rot and tropical ulcers.

COLLAGEN DISEASES

The various diseases of the collagen group are problems of tremendous interest and subjects of investigation in both fields of cardiology and dermatology. The dermatologist recognizes lupus erythematosus by the subjective symptoms and by characteristic objective cutaneous signs. The

cardiologist diagnoses the same entity by the same subjective complaints and by characteristic cardiac signs: namely, a verrucous, nonbacterial endocarditis; pericarditis with effusion; and other signs. We both seek confirmation from the laboratory. Too often, we speak of "acute lupus erythematosus" as being synonymous with "severe systemic involvement." Let me point out that the terms "acute," "subacute," and "chronic" are reference terms of time and duration. They have nothing to do with the degree of severity or sites of involvement. The inference should be clear.

In scleroderma and dermatomyositis, the signs and symptoms presented by the skin and contiguous tissues are more characteristic and of greater diagnostic value than are the cardiac signs and symptoms. Yet the myocardium is involved frequently in these diseases, decompensation may ensue, and electrocardiographic tracings will reveal varying degrees of nonspecific damage.

NEUROCUTANEOUS AND MISCELLANEOUS DISEASES

Our joint interest in the phakomatoses (or called by some the "neurocutaneous syndromes") can lead to a provisional diagnosis of the rare cardiac neurofibroma based on the recognition of minimal or great cutaneous evidence of von Recklinghausen's disease; or it may lead to the diagnosis of a cardiac rhabdomyoma in the child with the triad of epiloia: namely, tuberous sclerosis, convulsions, and adenoma sebaceum of the skin of the face.

Then, too, there is the genetically determined or congenital assortment of defects: for example, Hurler's syndrome or gargoylism, Marfan's syndrome, the various types of progeria or premature senile syndromes, and others in which both the skin and heart are involved.

Sarcoidosis is, of course, a disease exhibiting tremendous variation in manifestations. The skin, lymph nodes, lungs, liver, and bones are the organs most commonly involved, although any organ may be. The heart is involved in a primary way but rarely; the most common cardiac involvement is secondary to pulmonary sarcoidosis.

The hippocratic nail and terminal phalanx are well known; less appreciated is the mitral facies, a bright red cheek in a pallid face. May I also mention an interesting differential diagnostic finding in cyanotic states. In those patients with patent ductus arteriosus and pulmonary hypertension with dominant reversal of flow, cyanosis is more marked in the lower than in the upper extremities.

As further examples, the Rendu-Osler-Weber disease, pseudoxanthoma elasticum, and diffuse angiokeratoma corporis all have cutaneous and cardiac implications and manifestations.

COMMENT

Too often, dermatology is accused of being morphologic only, and dermatologists are accused of being morphologists only. Morphology is a strong attribute of our science still, but, in the younger generation of dermatologists especially, interest in morphology is not excessive. As all physicians do, we dermatologists use all our senses to study and perceive structure and form. We employ primarily the tactile and visual senses; cardiologists also still use the tactile and

visual plus the aural. By application of these facilities, we learn normal and pathologic function. We all use advances in technology and mensuration; for example, cardiologists use the roentgenogram and electrocardiogram; we, in dermatology, use the electromyogram, sweating tests, and tests of vasomotor function among others.

I now hope my point has been made. To you, Doctor Fahr and colleagues, may I express my deep and sincere appreciation for the honor you have given me and for the pleasure of being here today. After all, I trust I have proved the fact that physicians and doctors of medicine, regardless of our specialties or fields of practice, are brothers in and under the skin.

This paper was read on the occasion of the celebration of Dr. George E. Fahr's eightieth birthday, Minneapolis, January 27, 1962.

IDIOPATHIC FIBROUS OR FIBROMUSCULAR STENOSIS of the renal arteries occasionally is associated with hypertension, especially in young women. The non-atherosclerotic lesions are usually located in the middle or distal third of the artery and frequently involve the branches. Lesions are often bilateral, so repair or bypass of the renal artery lesion is recommended if possible. With unilateral lesions or other factors that make adequate repair unfeasible, nephrectomy should be done. Symptoms, if present, reflect prolonged high blood pressure and include hypertensive encephalopathy, coronary sclerosis, cerebral vascular insufficiency, and congestive heart failure. A continuous upper abdominal high-frequency bruit with systolic accentuation is characteristic. Arteriographic study reveals multiple areas of concentric narrowing of the renal artery with intervening areas of normal or dilated artery—giving a string-of-beads appearance and resulting from alternating fibromuscular thickening and zones of deficiency in the media and elastic tissue. Associated atheromatous disease of the abdominal aorta is rare. Isotopic renographic and separated renal function studies are also useful in diagnosis; excretory urography may be helpful.

Known duration of hypertension was six months to ten years in 17 female and 6 male patients with fibrous or fibromuscular stenosis of the renal arteries; 21 had surgery. A total of 19 were observed for six months or more postoperatively; 11 had had nephrectomy, 3 arterial repair, 3 arterial bypass, 1 heminephrectomy, and 1 exploration alone. Normotension resulted in 12 and 6 were much improved; the patient having exploration alone was not benefited.

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Fluoride Content of Municipal Water Supplies in North Dakota

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A DISCOLORATION of tooth enamel occurring in individuals drinking certain community waters was first noted by Black and McKay in 1916.¹ The fluoride ion was not identified as the causative agent until 1931.² Dental fluorosis, or staining of the enamel, occurs in those individuals whose daily intake is in the range of 2 p.p.m.^o to 4 p.p.m. fluorides.³ The optimum level of fluorides has been variously stated as that amount in the daily diet which falls between 1 and 1.5 p.p.m.⁴

Although there are no communities in North Dakota which have a fluoride content in their water supply high enough to cause detrimental effects to the health of its populace, certain areas have sufficient fluorides to cause fluorosis and mottling of the teeth.

In this study, 293 water samples from 155 North Dakota municipalities were assayed for their fluoride, iron, manganese, and sulfate content. An attempt was made to correlate regions of fluoride excess with mottling of teeth and to assess the relationship of fluoride content and depth of wells.

METHODS

One-quart polyethylene bottles were used to collect samples. These bottles were mailed to water plant operators with instructions to collect samples after allowing a few gallons of water to run from the well or tap. Samples were personally collected by the investigators in certain areas of high fluoride-containing waters.

The Scott-Sanchis⁵ method was employed during the early phases of this study since it is the method used by most municipalities in the state.

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The sensitivity of the method is about 0.1 mg. fluoride per liter water (0.1 p.p.m.).

It was found later that the Eriochrome Cyanine R method gave greater sensitivity.⁶ In the concentration range of 0.0 to 1.4 mg. fluoride per liter water, this method has a sensitivity of 0.016 mg. (0.016 p.p.m.). Sulfate ions may interfere with the assay and, in a number of determinations, steam distillation was necessary prior to the fluoride analysis.

The Spadn's method⁷ was used in the terminal phases of the study. It is slightly less sensitive than the ECR (0.05 mg./liter vs. 0.016 mg./liter) but has a less critical time requirement and requires less complicated instrumentation.

Close correlation was obtained between the Spadn's and ECR methods and the study suggests the use of the Spadn's method as a general assay procedure.

Manganese was determined by the persulfate method,⁸ sulfate by the turbidimetric method,⁹ and iron by the thiocyanate method.¹⁰

RESULTS

The content of fluoride, iron, sulfates, and manganese in certain state water supplies with 1 p.p.m. (mg./liter) of fluorides or more are listed in table 1. Fifty-five water supplies are in this category with the remaining municipalities having less than 1 p.p.m. fluorides, or slightly more in those cities fluoridating the municipal water supply.

The relationship of fluoride content to well depth is recorded in table 2. City waters with less than 1 p.p.m. fluoride have wells with an average depth of 121 ft. As noted in table 2, the deepest well with less than 1 p.p.m. was 1,307 ft. at Reeder, in the southwest corner of the state. This is a rare exception, in that the next deepest well was 480 ft.

There seems to be little correlation between

^oParts per million (mg./liter).

TABLE 1
FLUORIDE AND OTHER ION CONTENT OF CERTAIN MUNICIPAL WATERS IN NORTH DAKOTA

City	Well depth (feet)	Milligrams per liter			
		Iron	Manganese	Sulfate	Fluoride
Fullerton	1,090	.30	.1	145	1.03
Glenburn	202	.30	.0	185	1.07
Turtle Lake	421	.28	.0	10	1.19
Kenmare	320	.20	.0	121	1.20
Neché	16	.00	.0	201	1.22
Turtle Lake No. 3	420	.20	.0	30	1.26
Beulah	50	trace	.0	0	1.33
Goodrich	480	.36	.0	110	1.34
Bowbells No. 2	300	trace	.0	30	1.39
New Leipzig No. 1	820	.60	.1	30	1.42
Bowbells No. 1	220	.28	.0	0	1.55
Regent No. 2	800	trace	.1	45	1.68
Regent No. 1	500	trace	.1	53	1.69
Berthold	600	trace	.0	60	1.75
Bowman No. 2	1,060	trace	.1	210	1.78
Bowman No. 1	1,040	trace	.1	208	1.82
New Salem	347	.50	.0	271	2.01
Forbes No. 2	1,400	.10	.0	205	2.02
New Salem	357	.00	.0	325	2.09
Wahpeton No. 1	420	.00	.1	245	2.10
Forbes No. 2	2,000	trace	.1	190	2.18
Mooreton	243	.00	.0	1,227	2.19
Sheldon	479	1.95	.2	1,025	2.21
Fullerton	1,090	.00	.0	155	2.53
Elliot	1,200	trace	trace	1,050	2.68
Abercrombie	386	trace	.1	230	2.72
Flasher	175	1.50	.1	485	2.92
Casselton	317	.55	.0	1,267	3.00
Wahpeton	260	.00	.0	128	3.06
Columbus	289	.20	.0	25	3.14
Hebron	580	.00	.0	272	3.26
Glen Ullin	280	.10	.1	450	3.28
Flasher	435	.70	.1	340	3.32
Verona	1,170	.75	.1	1,000	3.48
Glen Ullin	269	.00	.0	700	3.50
Flasher No. 3	430	1.20	1.3	324	3.53
Cogswell No. 2	1,000	trace	.0	950	3.60
Cogswell No. 4	1,000	.45	.0	1,025	3.60
Scranton No. 1	1,140	trace	.1	180	3.69
Noonan No. 3	365	.00	.1	9	3.72
Wahpeton No. 2	260	.00	.0	23	3.72
Cogswell No. 1	1,000	.60	.0	900	3.74
Hebron	427	trace	.0	540	3.78
Devils Lake No. 3	1,500	.18	.0	1,075	3.92
Hettinger No. 3	1,100	trace	.1	55	3.95
Noonan No. 2	320	.00	.0	9	4.06
Mercer	585	.00	.0	10	4.30
Cogswell No. 4	1,000	1.20	.0	975	4.32
Hettinger No. 2	1,200	trace	.1	75	4.32
Cogswell	1,000	trace	.1	950	4.55
Hettinger No. 1	1,100	trace	.1	60	4.80
Verona	1,170	.20	.1	105	4.96
Richardton No. 3	590	trace	.0	45	5.30
Mott No. 2	420	.05	.0	50	5.48
Mott No. 1	378	trace	.1	45	5.80

well depth and fluoride content in those waters with more than 1 p.p.m. fluoride. However, as fluorides increase, the shallowest well depth also increases (table 2).

The results of a survey of school-age children in the areas of high fluoride-containing waters showed considerable mottling of the enamel where daily intake was known to exceed 2 p.p.m. fluoride. The two general areas in the state with high fluoride waters are the regions centered around Cogswell in Sargent County and Mott in Hettinger County (figure 1). Three other isolated areas adjacent to Noonan in Divide County, Devils Lake in Ramsey County, and Mercer in McLean County also have high levels of fluorides.

There appears to be no relation between well depth or fluoride concentration to the levels of iron, manganese, and sulfate.

DISCUSSION

The results obtained in this survey and an earlier study by Abbott in 1937¹¹ show numerous city or community water supplies with fluorides in excess. As the physiologic level of 1 to 1.5 p.p.m. fluoride is the optimum daily intake, then at least 45 North Dakota water supplies have sufficient

TABLE 2
RELATION OF WELL DEPTH TO FLUORIDE CONCENTRATION IN NORTH DAKOTA WATER SUPPLIES

Fluorides (mg./liter)	Number of samples	Well depth (feet)	
		Average	Extremes
0-0.99	185	121	15-1,307
1-1.99	16	521	16-1,090
2-2.99	11	736	175-2,000
3-3.99	18	657	260-1,500
4-4.99	7	911	320-1,200
5-5.80	3	463	378- 590

fluorides to cause dental fluorosis. However, the highest level of fluorides found are still much below that which in experimental animals produces osteosclerosis.¹²

Clinically, the excess of fluorides in certain waters presents primarily a cosmetic problem. Our results would indicate that wells of shallower depth generally have lower fluorides and should be exploited completely before deeper wells are used. Further, in certain areas where high fluorides are present, defluoridation may be considered, although the method appears to

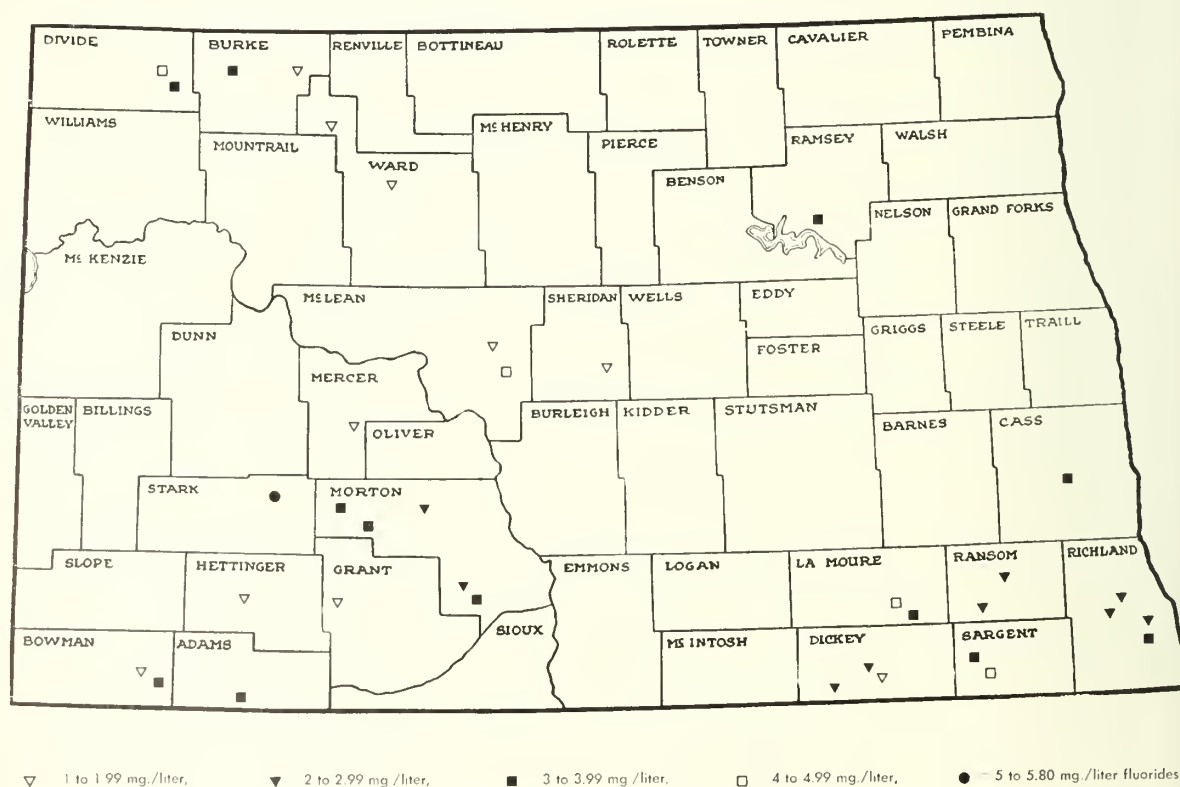


Fig. 1. Areas of high fluoride-containing waters in North Dakota

be rather expensive. Britton, South Dakota, has such a plant.

A further problem is the large number of communities with little or no natural fluorides. Measures might be taken to artificially increase their levels to 1 p.p.m. fluoride. It is incredible, in light of the overwhelming evidence in favor of fluoridation, that we still have opposition to its general use.

SUMMARY

An analysis of 293 water samples from 155 municipalities in North Dakota has revealed areas with no natural fluorides and others with sufficient amounts to cause dental fluorosis. The range

was found to be from 0.0 to 5.8 mg. fluoride per liter. Also included in this survey were levels of iron, sulfate, and manganese. Two distinct areas in North Dakota in the southeast and southwest parts of the state have high fluoride-containing waters. Dental fluorosis is prevalent among the population residing within this area.

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The authors wish to thank Dean T. H. Harwood and Assistant Dean A. F. Arnason, University of North Dakota School of Medicine, for their encouragement in carrying out this study. We wish also to thank the North Dakota State Health Department for their assistance.

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AEROSOLS are administered to the respiratory tract either to (1) mobilize bronchial secretions, (2) relieve bronchospasm, or (3) apply topical chemotherapy. High humidity is essential for liquefaction of secretions. Liquefaction is aided by addition of detergents or enzymes, but care must be taken to avoid irritation of the bronchial tree. Bronchodilator agents are added to the aerosol mists for asthma and emphysema. Epinephrine derivatives are helpful in relieving bronchospasm. Aerosol administration of antibiotic drugs may be useful if susceptible organisms are isolated from the patient's sputum or bronchial secretions.

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MEDICAL GRAND ROUNDS

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Fever

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Minneapolis

Fever is a mighty engine which Nature brings into the world for the conquest of her enemies.

THOMAS SYDENHAM

FEVER has been recognized as a cardinal sign of disease since the time of Hippocrates. After more than 2,000 years of experience with this obvious manifestation of illness, modern medicine cannot yet answer the question as to why sickness is so often accompanied by a rise in body temperature.

During most of this interval of some 2,000 years, fever had been recognized by touch. However, in the early seventeenth century, Sanctorius, an Italian professor, invented a crude clinical thermometer. In 1714, Gabriel Fahrenheit offered his mercury instrument for clinical use. The real start of medical thermometry, however, came as a result of one of the most extensive and methodical researches in the history of medicine. Beginning in 1851 and continuing for the next fifteen years, Carl A. Wunderlich systematically recorded the body temperatures of all patients admitted to his clinic at the University of Leipzig. He accumulated a huge number of readings on nearly 25,000 patients and eventually published a monumental monograph entitled "On the Temperature in Disease." He wrote in this monograph, "The conviction of the immense and almost incalculable value of the thermometer took fast possession of me; a conviction which I am bound to endeavor to wake and confirm in the minds of others."¹ Following this monograph, physicians in Europe and America began to employ medical thermometers.

NORMAL TEMPERATURE

Ever since Wunderlich's work, the normal body temperature has been considered to be 98.6° F.

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or 37° C. However, after reviewing some of his statistics, it is very evident that he did not consider 37° C. as the only normal temperature. Many extensive studies have been carried out since his time and have indicated repeatedly that the arrow on the clinical thermometer should be replaced by a band indicating a normal range.

In 1944, Ivy, while at Northwestern University, published a study in which he recorded the oral temperatures of 276 presumably healthy medical students one morning between 8 and 9 A.M.² The mean temperature in this group was 98.1° F. Two standard deviations on either side of the mean encompassed the range of 97.3° to 98.9° F. (figure 1). Wunderlich felt that the upper limit of normal temperature should be 99.5°. So if one were to eliminate the arrow on

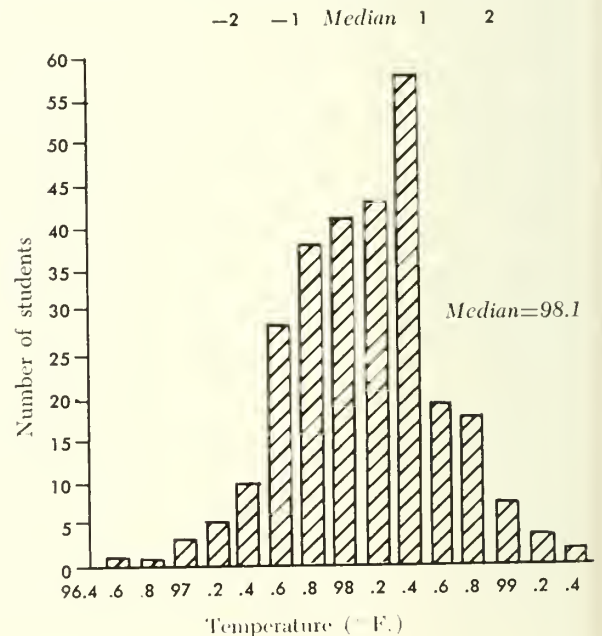


Fig. 1. Range of temperature of 276 healthy medical students measured between 8:00 A.M. and 9:00 A.M.

the clinical thermometer and substitute a band marked "normal range," Wunderlich's limits of 36.5 to 37.5° C. (97.2 to 99.5° F.) would be conservative and the limits of 36.2 to 37.8° C. (97.0 to 100° F.) liberal, but not excessive. Included in this range, then, would be the allowances for normal diurnal variation, individual variation, postprandial hypermetabolism or specific dynamic effect, the weather, and possibly emotional stress. Figure 2 summarizes the above data.³

When we measure an oral or a rectal temperature, we are measuring the temperature in that one area of the body only. As will be shown later, neither the oral nor the rectal temperature can be correlated in an interpretable manner with the blood temperature at the thermoregulatory center. They certainly cannot be correlated with the skin temperature and the temperature of the mass of subcutaneous tissue; these are usually much cooler than the rectal and mouth areas, and can change in either direction while the oral and rectal temperatures remain relatively stationary.

TEMPERATURE REGULATION

Nature has endowed the human organism as well as all the warm-blooded animals with an extraordinarily efficient system of thermoregulation. John Hunter was one of the first scientists to show that animals were able to resist external cold because they generated enough heat within themselves to counterbalance the loss. It is well known that in a cold climate the body speeds up its metabolic rate. It reacts to cold with exercise, shivering, unconscious tensing of muscles, and increased appetite. Sailors with a navy expedition to the South Pole consumed as many as 9,000 calories a day when doing hard work outside in the cold. At the same time cold increases metabolic rate, the body reduces heat loss to a minimum by cutting down the rate of circulation of blood to the skin. When the external temperature is hot, the body responds, on the other hand, by accelerating dissipation of body heat by increasing circulation through the skin, by sweating, and by faster respiration.

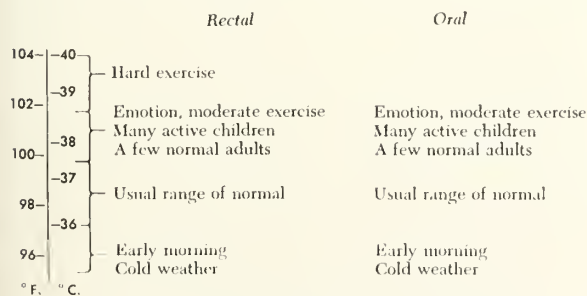


Fig. 2. Diurnal variation in temperature

When, in technology or in a living organism, a physical or chemical quantity is encountered that is maintained at a constant level against disturbances from the outside, one looks for a "servo-mechanism." A servo-mechanism needs 3 components. The chain of control begins with a *sensory receptor* which measures the variable in question. This measurement is then relayed to a *controller* which compares it with a set point to which the variable is to be held. Whenever the need arises, the controller sends instructions to an *effector mechanism* which carries out the necessary adjustments to bring the variable back to the point that is desired. Many servo-mechanism systems are known in biologic processes and are composed of the complex interrelationship of the nervous system, the circulation, and the hormones. It is pertinent to this discussion to outline what is known at the present time concerning the thermoregulatory system of the human being.

Receptor mechanisms. The general consensus for many years held that the primary temperature measuring organs and receptors were nerve endings in the skin and in the viscera. The end bulbs of Krause were considered to be the primary receptors of the sensation of cold, and the capsules of Ruffini were held to be the sites of heat perception. There was in addition, however, some suggestive evidence that a receptor center also existed in the central nervous system. Because of seemingly insurmountable technical difficulties, observations on the operation of sensory receptors in the skin and in the brain, reacting independently of each other, in the intact organism were not obtained until two years ago. No one apparently up to that time had succeeded in keeping 1 of the 2 sites at a constant temperature while observing the effects brought about by a temperature change in the other.

This approach called for technics to measure temperature in the human body at the two sites of presumed temperature reception, the skin and the hypothalamus, and some way to record rapidly and continuously the effective responses of vasodilation and sweating. By two ingenious arrangements, a group at the laboratory of the American Society of Heating and Ventilating Engineers in Cleveland were able to achieve this objective.⁴ Their special apparatus, called a gradient calorimeter, was able to respond rapidly and continuously to changes in the experimental subject and made it possible to record for the first time the total output of the effector mechanisms. The other innovation of this group was the development of a simple method of measuring the temperature near the hypothalamus.

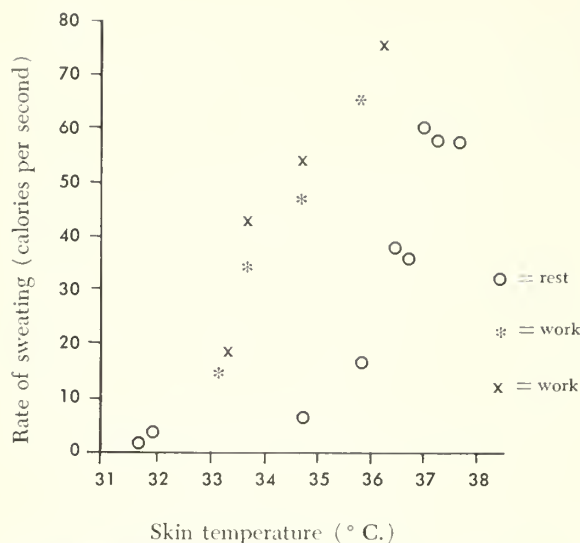


Fig. 3. Meaningless relationship between skin temperature and rate of sweating

They began their series of experiments by assuming that the rectal temperature gave an accurate picture, or record, of the actual "core" temperature of the body. However, after many experiments, it was not possible to make a correlation between the rectal temperature and the output of one of the effector mechanisms, namely, sweating. A similar meaningless relationship was found to exist between the measurements of skin temperature and the rate of sweating (figure 3). The results of these initial efforts "made sense only in terms of the classical notion that the thermostat in the interior of the body and the temperature sensing nerve endings in the skin have indissolubly interlaced effects upon the vasodilatation and sweating responses." However, by the seemingly simple expedient of introducing a thermocouple through the outer ear canal and letting it rest against the tympanic membrane, these "indissolubly interlaced" effects immediately became explicable (figure 4). The eardrum is near the hypothalamus and shares a common blood supply with it from the internal carotid artery. At the very first attempts, this group observed temperature changes associated with the eating of ice or drinking of hot fluids or the immersion of limbs in the warm water. Parallel measurements of rectal temperature did not show the variations at all.

The conclusion of the series of experiments conducted by this group was that a center in the hypothalamus trips the sweating mechanism at exactly the same temperature, no matter what is happening on the exterior of the body. They were able to prove conclusively that the thermo-

stat in the hypothalamus monitors the internal temperature of the body from the inside and hence itself is a temperature receptor. In the principal experimental subject of this group, the set point of the hypothalamic thermostat was 36.88°C . A change of as little as 0.01°C ., as measured at the eardrum, was sufficient to perceptibly increase the dissipation of heat through sweating.

Benzinger⁴ has called this temperature receptor end organ in the hypothalamus an "eye for temperature control comparable to the retina, the receptor organ for light." He points out that both of these "eyes" are derived from the same matrix, the bottom of the third ventricle of the brain.

The same degree of certainty about the nature of the mechanism which increases the body's metabolic rate in response to cold cannot be expressed at the present time. It appears that the 2 systems operate quite differently, and that, in the metabolic warming of the body, the temperature "eye" performs its task by inhibition of sensory impulses originating elsewhere.

Control mechanism. Ranson and his collaborators^{5,6} have performed the most definitive work delineating the main areas of temperature control in the brain. Two distinct regulating centers have been located in the hypothalamus. The center for controlling heat-loss functions such as sweating and panting (in the dog) is situated in the preoptic region of the hypothalamus, and a pathway from this center runs backward through the lateral hypothalamus. The center for protection against cold is located in the hypo-

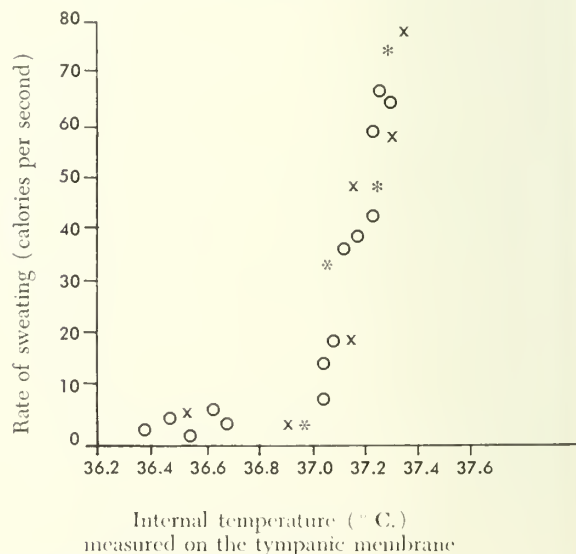


Fig. 4. Direct relationship between internal temperature and rate of sweating

thalamus proper, and its descending pathway also runs backward to the lateral hypothalamus. Bilateral lesions in the caudal part of the lateral hypothalamus interrupt both pathways and interfere with both the heat-loss and the heat-conservation mechanisms. Von Euler of the Nobel Neuro-Physiological Institute in Stockholm has succeeded in recording, in parallel with temperature changes, slow electric action potentials from the anterior area of the hypothalamus of cats.

The messages are received in these 2 areas of the hypothalamus from 3 sources. As pointed out above, the cells in these areas are directly responsive to the temperature of the local blood; in addition they receive direct connections by way of the lateral spinothalamic tracts of the spinal cord which carry the impulses from sensory receptors of the skin. Descending tracts from the cortex also enter the hypothalamus.

Effector mechanisms. The main effector mechanisms are the sweat glands, the blood vessels, and the skeletal muscles. The first 2 effector organs are innervated primarily by the autonomic nervous system. A great many of the responses originate directly in the hypothalamus, and messages are relayed not only to the effectors but to the higher conscious centers. It is evident that effector responses can be produced by conscious sensations; however, they are almost always mediated through the hypothalamus and the autonomic nervous system.

Responses by the hypothalamus need not always be neurogenic. As will be shown later, humoral factors in the blood stream can influence the neurons of the hypothalamus directly and produce responses in the effector system.

The responses of the effectors are limited. In case of pyrexia, the response is mainly sweating and dilation of the cutaneous vascular system. In response to cold there is shivering, vasoconstriction, and an increased tone in the skeletal muscle which increases heat production.⁷

THE EXPERIMENTAL PRODUCTION OF FEVER

Early speculations on the etiology of fever stress the notion that fever was caused by products of tissue destruction, and a search was instituted for a pyrexial agent in purulent exudate. Later, with recognition of the role of bacterial pyrogens or endotoxins in a variety of apparently unrelated fevers, investigation was focused on the biochemical and biologic properties of these agents. Only lately has there been renewed consideration of the body cells of the host as a possible cause of fever in both microbial diseases and those which are not associated with bacterial invasion.

The results of this work have confirmed older concepts that fever and inflammation are intimately related. Pyrogenic substances with similar properties have been detected both in inflammatory exudates and in the circulation during a number of experimental fevers, including those produced by bacterial endotoxins. Furthermore, granulocytes, the chief cells in purulent exudate, remain at present the only known source of these pyrogenic substances which appear to be mobilized within the host in response to a variety of injected agents. The most extensive investigations of the pathogenesis of fever have been carried out with bacterial pyrogens or endotoxins. An enormous literature has been devoted to the biochemical and physiologic properties of these agents.

Endotoxins have been isolated only from gram-negative bacteria and occur in nearly all types studied to date. Contrary to early reports, there is no direct correlation between virulence of an organism and its endotoxin potency. Endotoxins as a class have been characterized as complex, phosphorylated lipopolysaccharides of high molecular weight. These substances are nondialyzable and are markedly heat resistant, being inactivated only at temperatures above 160° C. for two hours.⁸

The active fraction of the lipopolysaccharide apparently resides in the lipid component. Many of these endotoxins have an extraordinary toxicity and pyrogenicity. The endotoxin from *Escherichia coli* in doses as small as .0001 gamma per kilogram are pyrogenic to rabbits, and doses as little as .0005 gamma per kilogram regularly cause fever in man.

The intravenous injection of endotoxin causes a regularly reproducible sequence of events in both laboratory animals and in man; however, endotoxin fever varies both in onset and pattern according to the species involved.

Among the responses to the intravenous injections of endotoxin, the following occur regularly in both rabbit and in man: (1) There is a latent period of from fifteen to thirty minutes before the onset of fever. (2) A high fever develops, with a peak at approximately four hours (see figure 5). (3) A prompt initial leukopenia follows. (4) Daily injections in all susceptible species produce a tolerance to the pyrogenic action. (5) After a rest period of about three weeks, a normal response can again be obtained on reinjection. (6) Tolerance is nonspecific, that is, there is no reaction even if a different endotoxin is used.

The tolerance that develops through the injections of bacterial pyrogens is a very curious

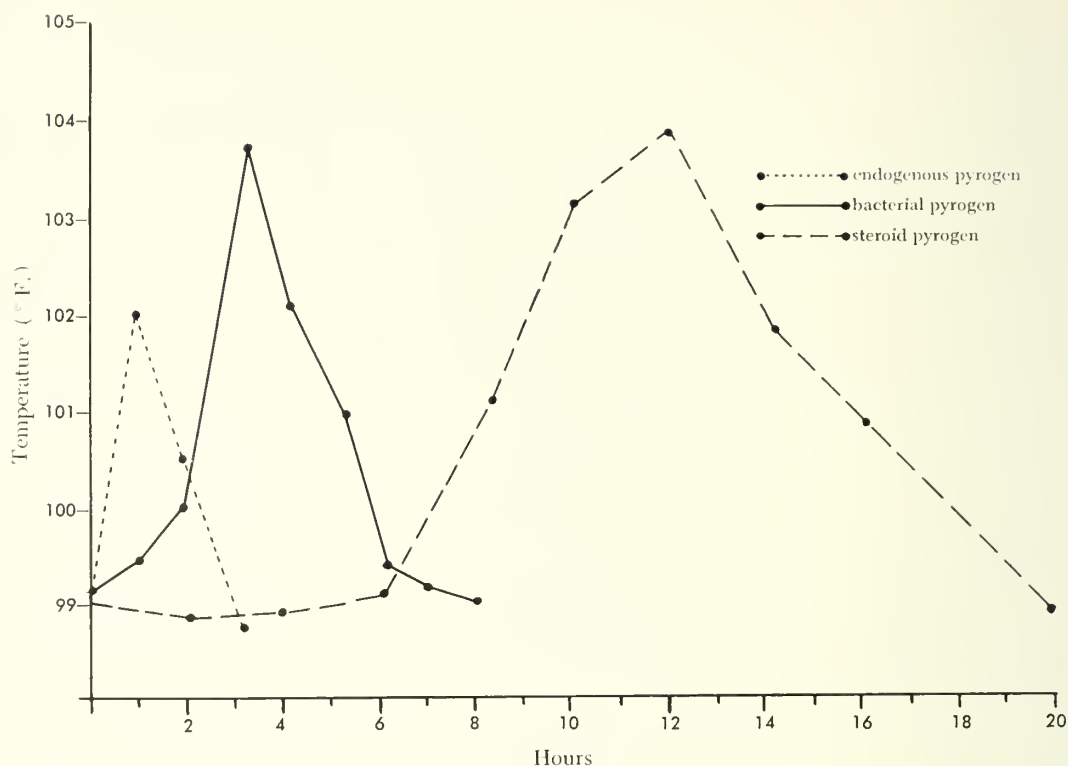


Fig. 5. Temperature response to the parenteral administration of the 3 types of pyrogen

phenomenon. It develops despite suppression of fever by antipyretic agents and does not appear after a series of mechanically induced fevers. This phenomenon is clearly separable from specific immunity as reflected in circulating antibody titers and can be demonstrated in patients with agammaglobulinemia. Beeson⁹ has concluded from his studies that tolerance is due to accelerated removal of the circulating endotoxins by the reticuloendothelial system. The toxic effects of endotoxin are not neutralized by precipitation with specific antibody, even in the zone of antibody excess.

Endotoxins seem to have both a direct and an indirect effect on circulating leukocytes, especially the granulocytes. Shortly after the injection of endotoxin, adherence or margination of the granulocytes along the capillary walls occurs. This probably accounts for the initial leukopenia seen after the injection of endotoxin. The indirect effect seems to be a promotion of the phagocytic ability of the granulocytes and an increased resistance of these cells to trauma. The most striking response to bacterial endotoxin, however, which may represent both a direct and an indirect effect on the leukocytes, is the production of what has come to be known as endogenous pyrogen.

Endogenous pyrogen. In the early 1850s, a German army surgeon, George Zimmerman, stressed the frequency with which elevations of body temperature are related to local processes of inflammation. A decade or so later, Billroth and Weber independently reported that pus from suppurative lesions when injected into cats, dogs, or rabbits frequently caused an immediate fever. The material used by Billroth and Weber was, however, never obtained from the same animal into which it was injected. This point was picked up by a medical student by the name of Frese, and he submitted for his doctorate thesis some work which extended the original observations. He injected pus obtained from both autologous and heterologous sources and was able to confirm the observations of Billroth and Weber in both circumstances.¹⁰

It seems then that these early workers demonstrated beyond a doubt the pyrogenicity of purulent exudate. However, one important question that they did not answer was whether or not the pyrogen was derived from the inflammatory cells of the host or from the contaminating bacteria in the pus. It was not until some eighty years later that an answer to this question could begin to be formulated.

In 1948, Beeson, working at Yale University,

detected in saline extracts of polymorphonuclear leukocytes prepared in such a way so as to exclude contamination from extraneous pyrogens, a pyrogen with properties very different from those of bacterial endotoxins.¹¹

Unlike bacterial endotoxins, Beeson's leukocytic factor was found to be heat labile and to produce a relatively brief febrile response characterized by a short latent period (figure 5). It caused little, if any, postinjection leukopenia, was fully active in bacterial pyrogen-tolerant recipients, and failed to produce tolerance when repeatedly injected. In addition, its action was shown to be at least to some extent species specific. The leukocytic pyrogenic factor has been shown to be a protein with a carbohydrate concentration of less than 1 per cent.¹²

The following is an outline of the brilliant experiments conducted by Wood, Atkins, Bennett, and King and their co-workers, in order to determine the source and mechanism of action of this endogenous pyrogen.¹² In 1953, Grant and Waland detected in the serum three hours after the injection of typhoid vaccine a transferable pyrogen which, when injected intravenously into a second rabbit, promptly caused a fever. In 1955, Wood and Atkins were able to show that the persisting pyrogen was quite separable from the bacterial endotoxin in the vaccine. This differentiation was accomplished by a method of passive transfer in which both normal and tolerant rabbits were used as recipients. The originally injected endotoxin was rapidly cleared from the blood stream, and the endogenous pyrogen persisted throughout the febrile response. Its concentration in the circulation was directly proportional to the intensity of the fever.

As indicated in the section above, bacterial endotoxins are known to have both direct and indirect effects on leukocytes. It was postulated that endotoxin-induced fever is caused by the thermogenic action of endogenous pyrogen released from leukocytes injured by the injected endotoxin. Both the relatively long latent period and the postinjection leukopenia which are characteristic of endotoxin fever are in keeping with this conclusion. Several recent studies have revealed that the formation of circulating endogenous pyrogen, following the injection of bacterial endotoxin, is greatly depressed in animals previously made leukopenic with nitrogen mustard.⁸

Whether or not bacterial endotoxin acted directly on the thermoregulatory centers of the brain had not been unequivocally ascertained until Wood and his co-workers set up an experimental model in which both endotoxin and

endogenous pyrogen were used.¹³ The experiment consisted of injection of both leukocytic and endotoxic pyrogens into the carotid circulation and into the venous circulation. A comparison was then made of the febrile responses following these injections.

Leukocytic pyrogen caused a more prompt and more pronounced febrile response when injected through the carotid artery than when injected intravenously. In contrast, bacterial endotoxin produced a delayed response which was exactly the same regardless of the route of injection. It was concluded that leukocytic pyrogen, when introduced into the circulation, acts directly upon the thermoregulatory centers of the brain, whereas circulating bacterial endotoxin acts by a different and less direct mechanism.

Recapitulation, then, of the above evidence leads to the following conclusions: Circulating leukocytes respond to the intravenous injection of endotoxin by sticking or adhering to the vascular endothelium. This form of cellular response has been shown to be characteristic of the earliest stages of acute inflammation. This "leukocytic sticking" regularly precedes the onset of fever and, as noted above, probably accounts for the postinjection leukopenia. The endotoxins in some way act upon the leukocytes, causing them to release the endogenous pyrogen. This substance, proceeding by way of the circulation, acts directly upon the thermoregulatory centers of the brain. It should be included parenthetically at this point that bacterial endotoxins may themselves act directly on the brain by spilling over into the spinal fluid. However, this mechanism appears to operate only under special circumstances, that is, following the injection of massive doses of endotoxin.

Wood and his group were well aware that the intravenous injection of endotoxin is not a satisfactory experimental model for the study of fever in general. It is relatively artificial in 2 senses. First of all, it involves a sudden intravenous injection of a highly toxic foreign substance, and second, it is complicated by the phenomenon of tolerance, which as far as is known, has no direct counterpart in natural fevers. In consequence of these facts, several experimental models designed to simulate more closely the conditions of naturally occurring disease were constructed. In 1956, Bennett¹⁴ reported a series of brilliant experiments on the fever of pneumococcal peritonitis in rabbits. During the active stage of infection, he demonstrated in the peritoneal exudate and also in the thoracic duct lymph a heat-labile substance with properties

identical to those of the leukocytic pyrogen. Its presence at both sites correlated closely with the animal's fever. He was, however, unable to detect the pyrogen in the blood stream. When defervescence was produced with penicillin, the pyrogen was no longer detectable in the exudate or in the lymph.

Wood was able to show that the heat-labile pyrogen obtained from this exudate was derived from the polymorphonuclear leukocytes and that these leukocytes were functionally active during the time of the discharge of this material into the surrounding medium. Using the passive transfer method again and considerably larger volumes of serum than were employed by Bennett, he was able to detect this pyrogenic factor, indistinguishable from leukocytic pyrogen, in the serum. From these results, it was evident that fever of pneumococcal peritonitis in rabbits was caused by circulating endogenous pyrogen produced by polymorphonuclear leukocytes in the peritoneal exudate and carried to the blood stream by way of the lymphatics draining the peritoneum.

There was, however, one criticism of the experiments of Wood, that being that bacteremia was present during the height of the fever. Although no pyrogen has ever been detected in pneumococcal cultures or extracts, it was thought advisable to perform analogous experiments under conditions uncomplicated by the presence of bacteria in the blood. These experiments were done in rabbits which were inoculated intradermally with a special strain of group A hemolytic streptococcus. The resulting cellulitis remained well localized and, although accompanied by high fever, was otherwise a relatively mild infection without detectable bacteremia. At the height of the fever, the same type of transferable pyrogen as observed in the pneumococcal experiments was found to be present in the circulation.

The above studies dealt exclusively with bacterial infections. Of course, fever is also present in viral infections. Atkins and his group at Yale University had been studying the relationship of virus infection and fever.¹⁵ This group discovered that following the intravenous injection of influenza viruses, an endogenous thermogenic factor which could not be differentiated from leukocytic pyrogen appeared in the blood stream. It is not presently known if this substance actually comes from the leukocytes or from some other source. It was found that this virus fever was not modified by nitrogen mustard-induced leukopenia and that such leukopenic donors appeared capable of producing normal amounts of

endogenous pyrogen following virus inoculation.

The origin of fever in hypersensitivity reactions is being investigated extensively at the present time. The various aspects of tuberculin-induced fever have been studied by Atkins and Hall.⁸ The evidence from their work indicates that the fever produced by the injection of old tuberculin into BCG-infected rabbits was mediated by a circulating pyrogen which was indistinguishable in its biologic effects from endogenous pyrogen obtained in several other types of experimental fever. They found that this material produced fever in normal recipients and was, therefore, clearly differentiated from old tuberculin itself which was pyrogenic only in sensitized animals.

Yondel has reported a series of beautifully designed experiments on the mechanism of febrile transfusion reactions.⁸ He has postulated that, under conditions of immune hemolysis, antigen-antibody complexes are released which alter the surface properties of leukocytes in such a way that they agglutinate and release endogenous pyrogen.

Investigation of the cause of fever in serum sickness has also been carried out. It seems that the intravascular combination of antigen with antibody and the subsequent production of cellular damage stimulate the release of endogenous pyrogen in a similar manner to that seen in other hypersensitivity reactions. The question as to whether the antibody that is involved is circulating or fixed has not been settled. It seems that once again the species of experimental animal plays a role, as there seems to be a difference in response between rabbits and guinea pigs.

PYROGENIC STEROIDS

One of the most exciting recent developments in the search for the cause or mechanism of production of fever has been the discovery of the capacity of a number of steroid hormone metabolites to provoke fever in man. These pyrogenic steroids belong to a class of compounds previously considered to be devoid of biologic activity. These steroids include 19- and 21-carbon compounds of both the 11-desoxy and 11-oxygenated series; they all have the 5-beta configuration. They are all derived from endogenous adrenal and gonadal hormones, and they represent the first pure substances of known chemical structure and physiologic origin which exhibit consistent pyrogenic activity in man. The response in the human being to the intravenous injection of these steroid metabolites is distinct from that produced by bacterial pyrogens or

endotoxins and from that produced by the endogenous pyrogens.

Kappas and his group^{16,17} at the University of Chicago have been the pioneers in the investigation of steroid pyrogen fever. The chemical prototype for substances with this thermogenic activity is the metabolite etiocholanolone (figure 6). This 19-carbon steroid originates from several precursors including androgenic hormones produced by the testes and the adrenal cortex.

Following injection of this substance, there is a latent period of four to eight hours before the temperature rises; the temperature reaches a peak at approximately twelve hours and generally subsides within twenty-four hours.

There is a significant leukocytosis which generally parallels the course of the temperature elevation. This is in contrast to the profound leukopenia which is characteristic of endotoxin fever (figure 5). This response is consistent and reproducible. Repeated injections do not produce tolerance to this agent. There seems to be a rather high degree of species specificity to the steroid-induced fever. Injection into 11 different species of laboratory animals produced no response. Endogenous pyrogen derived from leukocytes has not been found in the serum following the injection of the steroid pyrogens.

The pyrogenic action of etiocholanolone can be changed by certain alterations of the molecules which are known to occur in vivo. Esterification of the compound results in complete elimination of its fever-producing activity. The in vivo counterpart of this chemical alteration is conjugation of the free steroid with glucuronic acid. This process undoubtedly accounts for the fact that etiocholanolone, which is produced endogenously, is not pyrogenic in man under normal circumstances.

The addition of an oxygen molecule in the 11 position of the steroid structure produces a substance which has a somewhat lesser fever-producing capacity than etiocholanolone itself. This substance does not represent a metabolite of etiocholanolone or of the androgenic hormones. Rather it is derived in vivo from hydrocortisone. It has a significant degree of pyrogenicity and presents the interesting paradox of a fever suppressing hormone being metabolized in part into a fever-producing end product.

The pyrogenic effect of the 19-carbon compound, etiocholanolone, extends to 21-carbon steroids having the 5-beta configuration as well (figure 6). Examples of these related C-21 steroids are pregnanolone and pregnanediol. These 2 compounds are the principal metabolites of

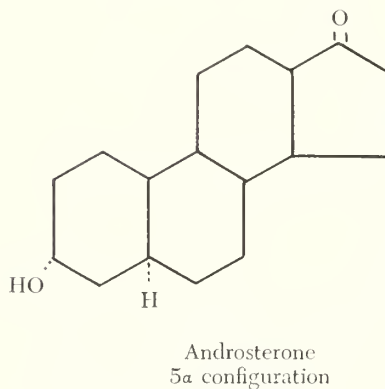
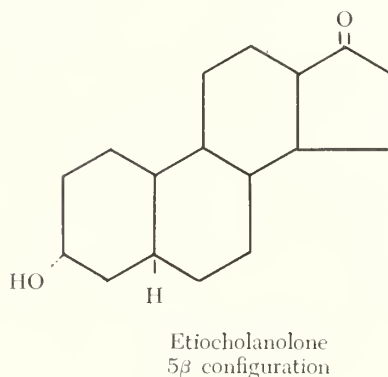
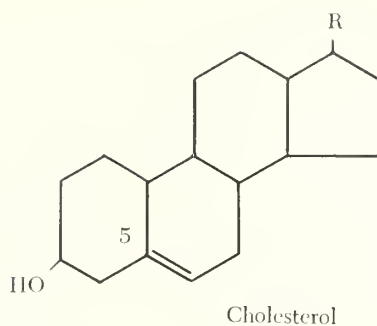


Figure 6

progesterone, a hormone that has been shown to have a slight temperature-elevating activity of its own. The capacity of these 2 substances to produce fever is changed by the same chemical alteration shown to influence the activity of etiocholanolone.

The means by which these pyrogenic steroids provoke fever in man are not clear. There are several facts, however, which are known concerning the fate of these substances when injected intravenously. First of all, there is no significant alteration in the steroids following administration. For example, following injection

tion into man, etiocholanolone is recovered unchanged and nearly quantitatively in the urine. Second, the half-life of the intravenously administered steroid in the form of free compounds circulating in the blood is well under sixty minutes. Thus, during the period of development and peak of fever, the free steroid pyrogen cannot be identified in the plasma.

There are several important observations and, perhaps, conclusions that can be gathered from the data concerning these pyrogenic steroids. First of all, it is evident that these steroids belong to a class of compounds previously considered to be devoid of biologic activity. Second, since these compounds are transformation products of hormones, the probable existence of as yet unrecognized biologic activity among other steroid hormone metabolites is implied. Third, the endogenous origin of the steroid pyrogen naturally stimulates speculation regarding its possible participation in the pathogenesis of fever in man under various circumstances. An interesting observation along this line has recently been made by Tisdale and associates at Yale.¹⁸ While studying the fever of patients with active, uncomplicated Laennec's cirrhosis, they discovered unconjugated etiocholanolone in their urines. Finally it is evident that the established chemical structure of these pyrogens, their availability as pure compounds, and the consistency with which they provoke fever all combine to provide a safe and useful experimental tool for the study, directly in man, of the pathogenesis of fever.

ETIOCHOLANOLONE FEVER: A CLINICAL ENTITY

In 1958, Bondy and his co-workers reported 2 patients with recurrent attacks of fever, abdominal pain, arthralgia, hepatomegaly, and leukocytosis unassociated with any recognizable infection or inflammatory process. During their attacks of fever, the only urinary 17-ketosteroids these patients excreted in appreciable quantities was etiocholanolone. At the same time, unconjugated etiocholanolone was found in their plasma. Between attacks, no etiocholanolone was found in the plasma, and the urinary 17-ketosteroid pattern was normal. In 1960, this group reported 4 additional patients in whom similar findings occurred.¹⁹

The first hypothesis which this group attempted to resolve was related to the possibility that the steroid plasma levels and urinary excretion patterns were nonspecific effects of fever in general and were the result of fever rather than its cause. Twelve patients with fever of known etiology, ranging from bacterial pneumonia to

cholecystitis, were investigated and in none of them could significant unconjugated etiocholanolone be demonstrated in the plasma. The second problem that they attempted to solve was to determine whether or not increasing the amount of endogenous etiocholanolone in the body would cause an attack of fever in a susceptible individual. Experiments along this line showed that the administration of large amounts of precursors of etiocholanolone did not produce fever or elevate the concentration of unconjugated etiocholanolone in the plasma. However, the injection of a pyrogenic steroid, 11-keto-pregnanolone, caused an impressive fever; as the fever rose, large amounts of unconjugated etiocholanolone were demonstrable in the plasma. Since 11-keto-pregnanolone itself is not a normal precursor of etiocholanolone, it seems the increase in urinary and plasma etiocholanolone must have reflected a change in the metabolism of steroids.

Their group of 6 patients can be described as follows: All the patients were males ranging in age from 10 to 48 years. Their attacks of fever occurred cyclically and regularly at periods of three to four weeks. All were in good health between attacks, even though 1 patient had had the disease over a period of twenty-six years. Some had relief of symptoms with corticosteroid treatment, although treatment with ACTH often made matters worse. None had evidence of amyloidosis. The racial backgrounds of these patients were varied; 1 individual was a Negro. In 5 instances there was no clear history of involvement of other members of the family. Bondy and his group therefore feel that this disorder represents a new clinical entity that is different from the syndrome of intermittent fever described by Heller as Familial Mediterranean fever. The differences between the 2 types of disease are shown in the following table.

	<i>Familial Mediterranean fever</i>	<i>Etiocholanolone fever</i>
Mediterranean origin	+	—
Regular cyclic fever	—	+
Improved by steroids	—	+
Amyloidosis	+	—
Aminoaciduria	+	?
Unconjugated plasma etiocholanolone	—	+

In order to explain this disorder, 2 defects have been postulated to exist in the body. Both of these defects probably reside in the parenchymal cells of the liver. The first defect is prob-

ably an aberration in the conjugation of etiocholanolone with glucuronic acid. The second defect may well be an abnormality of the steroid reductases which catalyze the reduction of the double bond on the steroid ring to produce in 1 case 5-beta steroids such as etiocholanolone and, on the other hand, 5-alpha steroids such as androsterone. The acute attacks of etiocholanolone fever may be associated in some way with the decrease in the activity of the 5-alpha steroid reductase and the concomitant increase of the 5-beta reductases. It is felt that corticosteroids prevent attacks of fever by reducing the secretion of etiocholanolone precursors.

FEVER AS A MECHANISM OF RESISTANCE

In a rather comprehensive review of the subject of fever as a mechanism of resistance, Bennett and Nicastra²⁰ came to the conclusion that it is impossible to say at the present time what role fever plays in resistance. They point out that most of the studies have been done with animals and that it is impossible to transfer the results from these animals to the human system. It is noted that fever might influence resistance to infection in 2 ways: first, by direct thermal effects on the microorganisms or their products or, second, indirectly by thermal alteration of one or more of the various cellular and humoral mechanisms that are responsible for resistance to infection. There is little or no evidence to indicate that in the human being either one or both of these effects take place.

SUMMARY

1. As with most other biologic quantities, normal temperature must be represented by a range rather than by a single value.
2. The thermal regulatory system can be envisioned as a servo-mechanism.
3. The hypothalamus contains a temperature receptor as well as the controlling centers for temperature regulation.
4. Bacterial endotoxins produce fever by injuring leukocytes, which in turn release an endogenous pyrogenic substance, and by a second and as yet unknown means.

5. The endogenous pyrogen released from leukocytes acts in some way directly on the thermoregulatory centers in the hypothalamus.

6. A new class of substances, which are metabolites of endogenous hormones previously thought to be devoid of biologic activity, have been found to be pyrogenic in their unconjugated form.

7. A new clinical entity, etiocholanolone fever, has been shown to exist and to be probably related to some intermittent defect in steroid metabolism or conjugation.

8. The role of fever in resistance to infection is unknown at the present time.

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Friend and Faithful Guardian of Community Health

Charles L. Sherman, M.D.

J. ARTHUR MYERS, M.D.

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IT COULD ONLY happen once in a lifetime as it did to Dr. Charles L. Sherman, who was nominated "General Practitioner of the Year" by the Minnesota State Medical Association as their candidate for the state's centennial observance in 1958.

Dr. Sherman can be thankful that his ancestors were of sturdy Swedish-Norwegian stock, for, during his more than sixty years as a general practitioner in Minnesota, he was to "squeeze all the energy possible from the human body"—his body—and, from his stoic inheritance, he always got the one more drop of endurance to help a sufferer. Luverne, a community in southwestern Minnesota, is Dr. Sherman's home; but his interests and faithful service over the years were not limited by any boundary lines and covered more than the 8 surrounding counties.

Now, after his long stint of service, Dr. Sherman, at 84, has announced his retirement. However, Luverne is still to be his home. How complete his retirement will be is a matter of speculation in the community as well as elsewhere. After he and Mrs. Sherman return from a vacation, rumor has it that he will see patients in the study of his home.

Charles L. Sherman was born November 11, 1876, in Canton, South Dakota, the same year Alexander Bell invented the telephone. It has been the jingle of the telephone that more often than not broke into his slumber and sent him, in good and bad weather, to answer the call of the sick.

Young Sherman attended the grade and high schools of Canton. After graduation in 1896 from Augustana College in Canton, he broke from his home town for the first time, going to Barnes Medical College in St. Louis. He received his M.D. degree in 1900 and set up his first practice in Farmersburg, Iowa, where he remained for four years.

EARLY YEARS OF PRACTICE

The year 1904 brought a change in his life. With his wife, three-year-old daughter, and infant son, he moved to Luverne in Rock County, where he has resided ever since. It was a small town in which Dr. Sherman took up practice and assumed the responsibilities of a "horse and buggy doctor." It was rugged going at first. He set up an office in the "walk-up" second story of a building on the main street.

According to an account by Dr. Sherman, it was about one week before he received his first patient. Here again, his ancestry stood him in good stead, for the patient was a young, immigrant, Norwegian farmer named Tobias Thorson, who could speak little, if any, English. The boy had a painful boil on his wrist which the doctor lanced and treated. Some fifty years later, the same patient reminisced about that first meeting at Luverne's Doctor Sherman Day celebration held in the fall of 1953. Since the first call, Mr. Thorson has visited Dr. Sherman twice a year. The first call netted Dr. Sherman fifty cents, the office call charge at that time.

It was not long before the new doctor gained the confidence of the community and his practice grew steadily. Dr. Sherman, his horse and buggy, and his boon traveling companions—his OB bag and his regular medicine bag—became familiar sights in and about Luverne. It seemed that "Doc" Sherman was continually on the go, caring for patients day and night.

While compiling data on Dr. Sherman, Lyall A. Schwarzkopf, of the Minnesota State Medical Association staff, retold some of the doctor's experiences of the early days:

"Once in the spring of the year, the doctor was called to a home out in the country. In order to get

to the home, he had to cross the flooding river just outside of town. With no other course available, he urged the horses into the stream. Everything went well until he looked downstream and saw both his OB bag and medical bag floating down the river. Fully clothed, he jumped into the river and retrieved the bags."

Another story concerning a country delivery went like this:

"It was winter, cold, and the snow was deep. The sleigh tipped over three times on the way to the farmyard. When Dr. Sherman got there, the woman was ready to deliver. He asked the farmer for a kettle to boil some towels, but the only thing in the house was a wash basin. The towels were very dirty, so he had to use lye salt in boiling them, and, just as the woman was ready to deliver, the kerosene lamp burned out. Because of his wife's condition and the bad weather, the farmer had not been able to go to town for more oil, so the doctor sent his boy driver out for the lamps on his sleigh. The baby, who was born by sleigh lamplight, is a healthy grandmother today."

Dr. Sherman, who was quick to take to new things, in 1906 had the distinction of being the first person in Rock County to buy a Ford. The car was a "Tin Lizzy," with a dry-cell ignition, no windshield, and no top.

When the children were still young, tragedy struck the happy family with the death of the doctor's wife from pulmonary tuberculosis. Her death spearheaded his already active interest in the study of tuberculosis. He found that other members of his wife's family had died of the disease or had suffered from it. Also, tuberculosis was the cause of many deaths in the community.

Through untold effort, Dr. Sherman was instrumental in getting the 8 county boards in the southwestern part of Minnesota to establish a tuberculosis sanatorium. In 1914 a sanatorium board was organized to build and conduct the sanatorium. Dr. Sherman was named to serve from Rock County and was elected its first president.

It was at this time that Dr. Sherman's 18-year-old daughter was also stricken and died from tuberculosis. In spite of his personal grief and the ever-increasing load of his general practice, Dr. Sherman gave unstintingly of his knowledge and experience in the fight against tuberculosis. During 1917, the year the sanatorium opened at Worthington, there had been 64 deaths from tuberculosis in the 8-county area. A group of 56 patients was admitted to the sanatorium, but the list of applications for entrance was longer because of lack of accommodations for more.

There now arose the need for a medical director for the sanatorium, and it was here that Dr. Sherman met young Dr. Sidney A. Slater. This was the beginning of an association which lasted until the death of Dr. Slater in 1959. Both physicians had before them the vision of tuberculosis control and final

eradication. No one knew the problems better than this pair of experts whose perseverance in disseminating facts concerning the disease and whose hard work in administering programs are now recorded history in tuberculosis control achievement. Dr. Slater himself had contracted clinical tuberculosis soon after he was graduated from the Medical College of Virginia, Richmond. When he recovered, he served as medical director of Grand View Sanatorium, Oil City, Pennsylvania, until going to Worthington. Dr. Slater assumed his duties as medical director of Southwestern Minnesota Sanatorium in Worthington in 1919, a position he held until his retirement in 1957.

Years after he came to Minnesota, Dr. Slater has been quoted to have said: "I wouldn't have come to Worthington if it hadn't been for the persuasiveness of Sherman. When things got rough during a board meeting, Sherman was the diplomat who brought harmony back into the meeting." Dr. Slater's admiration for Dr. Sherman was abiding. Until the day of his death, there was nothing within his power that he would not do in support of Dr. Sherman and his work.

At the turn of the century, most of the hospitals in small towns were owned and operated by physicians. In Luverne, a white frame house served as the hospital and was owned and operated by Dr. A. E. Spaulding. Not long after Dr. Sherman went to Luverne, he was invited to assist Dr. Spaulding with surgery cases. This relationship continued until the death of Dr. Spaulding a few years later. The 17-bed hospital was then purchased by Dr. Sherman and Dr. Charles O. Wright and was operated by them until Dr. Wright died in 1930. Dr. Sherman continued to administer the hospital until 1945, when he found it too great a task to carry on its administration in addition to his many other projects. After he sold the hospital to the city of Luverne, he found himself serving its needs again as president of the board. In 1957, a new hospital was completed, with Dr. Sherman contributing heavily as well as serving as an ardent worker in the campaign for hospital funds.

Dr. Sherman always has kept up with the latest developments in the field of medicine. Between his calls on the sick, he was usually to be found seated near the telephone with a book in his hand. He was always on hand when there was a meeting at which he could lend support to a worthy cause, whether it be in the field of medicine, business, or education. One of his greatest interests was eradication of tuberculosis, which he had witnessed take so great a toll in killing or handicapping the lives of his family, patients, and friends.

When Dr. Slater began the new tuberculosis case-finding methods at Southwestern Minnesota Sanatorium, it was with the greatest approval of Dr. Sherman. From this project, Dr. Slater wrote over 1,000 case histories for the area and published the findings. Dr. Sherman, in 1921, gained consent from

the schools to give pupils tuberculin tests. Chest x-ray films of the reactors were taken at the sanatorium, and the sanatorium also offered medication and a place where active cases could be isolated, thus breaking the chain of infection.

Dr. Sherman could be termed a "joiner." He affiliated himself with every organization and group with interests that were for the good of his community, his state, and his country. Townsfolk tell that after "Doc" had well passed the age at which the average man retires, he never failed to accept a request to serve on a committee or campaign where he thought his advice might add in some way to the success of the venture. A former mayor of Luverne recently told of such an incident: "In 1955, when Dr. Sherman was around 80 years of age and busier than most men in town, I asked him to serve on a certain advisory committee. He accepted without question. He has given unstintingly of time and resources to numerous community activities over the years. His views and advice have been sought and are highly valued by myself and by many others who have been active in civic affairs."

Dr. Sherman has always been a one-man chamber of commerce for his town. The progress of the community and the care of its sick were always first with him. During his eighteen-year term as president of the Rock County Bank, he helped many men get started in business. He was also instrumental in building and encouraging new business in Luverne. Many Luverne students credit Dr. Sherman with providing the means and inspiration for them to complete the college courses that prepared them for successful careers. Dr. Sherman, they say in Luverne, is a "big doer of good, but a small talker." He exemplifies the true humanitarian.

HONORS AND ACHIEVEMENTS

It has been a long time since the new doctor in Luverne was put through the gauntlet of trials to prove his worth. Today he is "Doc," the friend and faithful guardian of the health and well-being of the community; he has passed the tests. On many occasions, recognition has been given him for his dedicated service by loyal citizens, friends, and organizations. Among the most gratifying to him must be the appreciation of the people for his unflagging efforts in the prevention and control of tuberculosis. The leadership and work of Dr. Sherman, matched by that of Dr. Slater, paid off when it was announced in 1941 that Lyon County, one of the 8 in the sanatorium area, was the first of Minnesota's 87 counties to be accredited. Soon all 8 were accredited by standards of the Committee on Tuberculosis of the Minnesota State Medical Association, the Minnesota State Department of Health, and the Minnesota Tuberculosis and Health Association.

Governor Edward J. Thye lauded Dr. Sherman and Dr. Slater for their great work in tuberculosis control back in 1943 at a State Board of Health conference in Luverne. Dr. Sherman has the distinc-

tion of having served as president of a sanatorium board longer than any other man in Minnesota; he headed the Southwestern Minnesota Sanatorium board for forty-four years.

When the residents of Luverne celebrated "Doc Sherman Day" in September of 1953, hundreds of people gathered, including a third generation who could call themselves "Doc Sherman's babies." During his service as the "family doctor," some estimate that he has helped to deliver 3,000 babies. When he went to Luverne, the population was 2,500 and is now more than 4,000, so the number of babies that Dr. Sherman has delivered amounts to double the population of the town when he came.

The Minnesota Public Health Association awarded Dr. Sherman a life membership in 1938 in recognition of his long and faithful service in the fight against tuberculosis. An inscription described him as "pioneer leader in the campaign to eradicate tuberculosis and able assistant in the state and national effort to protect humanity."

In 1927, Dr. Sherman was appointed to the Minnesota State Board of Medical Examiners. Thereafter, he was reappointed continuously for thirty-two years regardless of the political party of the governor. That was the longest period ever served by any physician. During this long time of service, he missed only 3 board meetings. He is known for his great interest in encouraging younger men in the medical profession and as a staunch fighter to keep its standards at the top in Minnesota.

Dr. Sherman was honored at another fiftieth anniversary celebration on January 16, 1958, for his fiftieth year of serving as a Worshipful Master of the Masonic Lodge. He is a past commander of Luverne's Commandery Nights of Templar, a past Chancellor of the Knights of Pythias, and a member of the Shrine.

Dr. Sherman is also registered as a hospital administrator, with a certificate from the State Board of Health in 1957. He was rejected from service during World War I, but did serve as an examining physician. During World War II, he was local and district examiner. He was made medical advisor to Selective Service in 1948. He is credited with being one of the organizers of the Luverne Rotary Club and is a former president of the Kiwanis Club and the Commercial Club. He has served as Rock County health officer, coroner, and city health officer. As health officer during the influenza epidemic of 1918 and 1919, he worked constantly with little or no rest. Although he taxed his endurance almost to the breaking point, he avoided contracting the disease.

Dr. Sherman has always been a faithful worker in medical societies. Before going to Luverne, he joined the Iowa State Medical Society. On his arrival in Minnesota, he became a member of the Sioux Valley Medical Society in which he served as an officer. He is a 50-Year Club member of the Minnesota State Medical Association and a member of the American Medical Association, the Southwestern Minnesota

Medical Society, and the Southern Minnesota Medical Association. Dr. Sherman was one of the 21 persons who helped organize Blue Shield in Minnesota.

Patients and friends describe Dr. Sherman as a quiet man who may seem brusque to people who do not know him well. But, when in conference or treating the sick, he is said to be "the most tender man."

When word was out that "Doc" Sherman was to retire, the town's newspaper columnist, Al McIntosh, wrote in the *Star-Herald* about some of the facts that made him their beloved doctor. He described the office which the doctor had occupied for more than fifty years in which hangs the famed old picture of "The Doctor:"

"You all know that picture—the little girl, desperately sick, lying amidst the fever-tossed bed clothes. In the background, dimly lit by the feeble light of dawn coming through the window, is the father, the anguish of worry carving his face deep with lines of care. The mother is sitting on a chair, her head

resting on the table, exhausted by anguish and loss of sleep.

"And the doctor—the noble figure—sits in the chair, leaning forward, his chin propped up in his hand as his eyes watch every little movement of the sick girl.

"In my book—and it wouldn't take much changing of the picture—you could easily have an artist paint in Dr. Sherman's likeness in that picture. The scene has been re-enacted thousands of times in Rock County, and times beyond count Dr. Sherman has sat the night through beside the bed of some desperately sick man, woman, or child.

"In over sixty years of practice, it would be impossible to count how many people owe their lives and their happiness to this devoted practitioner of medicine."

It is easily understood why there were so many eager workers for Minnesota's doctor of the centennial year—Charles L. Sherman.

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The author wishes to thank Miss Dorothy Riley for her assistance in the preparation of this manuscript.

IN VIVO RELEASE of serotonin into platelet-free plasma can be detected within fifteen seconds of rapid injection of *Escherichia coli* endotoxin into rabbits. Magnitude of immediate released serotonin is greater with 1 than with 0.05 mg. of endotoxin per kilogram of body weight, but larger doses do not have a further enhancing effect. Plasma concentration of serotonin does not notably rise because of release induced by nonlethal doses of endotoxin. Administration of 4 mg. of *Esch. coli* endotoxin per kilogram—a uniformly lethal dose—produces a more sustained elevation in plasma serotonin content.

R. B. DAVIS, W. R. MEEKER, JR., and W. L. BAILEY: Serotonin release by bacterial endotoxin. *Proc. Soc. Exper. Biol. & Med.* 108:774-776, 1961.

PROLONGED AND PERHAPS PERMANENT SURVIVAL of skin homografts occurs in some rats with induced vitamin B₆ deficiency, even after a return to normal B₆ intake. A likely explanation is that the graft, when protected over a critical period, becomes less antigenic or less responsive to antibody. Survival apparently is not due to (1) persistence of vitamin deficiency, (2) acquired tolerance, (3) complete inability of the skin to respond to antibodies, or (4) incorporation of skin into host tissue.

B. FISHER and E. SCHEWE: Further observations on skin homografts in pyridoxine deficient animals. *Ann. Surg.* 155:457-464, 1962.

Book Reviews . . .

Metabolic Effects of Anesthesia

S. H. NGAI, M.D., and E. M. PAPPER, M.D., 1962. *Springfield, Ill.: Charles C Thomas*. 89 pages. \$5.75.

Descriptions of metabolic changes during general anesthesia in man and in the animal are reviewed and possible mechanisms for the changes described are given. The authors discuss metabolic rate, carbohydrate and protein metabolism, and liver, kidney, and endocrine function.

In the second section of the monograph, the basis of respiratory acidosis during anesthesia and its effects on various systems of the body are discussed. The data impress the reader with the unreliability of many of the findings that have been presented in the past.

The volume is well indexed, and a fine bibliography of 367 references is included. This is a book that causes one to think and to be more critical of the material that is being put into print today. However, one seeks in vain for more information on the subjects of circulation and, particularly, cardiac function.

This book illustrates the value of the critical review of a subject and should be read with great interest by all who are concerned in the practice of administering anesthetic agents.

JOHN S. LUNDY, M.D.
Chicago

Atlas of Clinical Endocrinology

H. LISSER, M.D., and ROBERTO F. ESCAMILLA, M.D., second edition, 1962. *St. Louis: C. V. Mosby*. 489 pages. Illustrated. \$23.00.

This book, as the name implies, is an atlas of endocrinopathies. The popularity of the book is attested by the fact that a second edition has followed the first within a five-year period. The vast clinical experience of the authors has been put to good use by the illustration of a complete spectrum of representative cases in a most concise manner. Diagnosis and treatment are not ignored. The authors have indeed brought bedside teaching to the clinician by their novel manner of presenting authenticated cases of common and uncommon endocrine disorders and including syndromes simulating endocrinopathies. The book is divided into sections covering the disorders of the various glands of internal secretion, such as pituitary, thyroid, parathyroid, adrenal, islet cells of the pancreas, testes, and ovaries. Sections on hypothalamic obesity, true hermaphroditism, and the new syndrome of multiple endocrine adenomas (Zollinger-Ellison syndrome), are also included. Of particular value is the section on nonendocrine disorders which so frequently have been stamped as endocrinopathies: mongoloidism, Laurence-Moon-Biedl syndrome, gargoylism, the Stewart-Morel-Moore or Morgagni syndrome of hyperostosis frontalis interna, and many dyschondroplasias, such as achondroplastic dwarfism, and Morquio's disease. The last section of the book is presented under the heading of Appendix and includes a variety of useful information from normal values for laboratory tests to height-weight curves for the various age groups.

Altogether, this is a most satisfactory book for student and practitioner alike. There is but one criticism this reviewer has to offer. Such an atlas is inclined to make specialists (endocrinologists) out of clinicians should they simply match appearance with illustrative examples and thus satisfy their search for a diagnosis and license for treatment. The true purpose of this excellent book is to serve the clinician without training in the highly specialized field of endocrinology by helping him to recognize endocrinopathies.

ROBERT B. GREENBLATT, M.D.
Augusta, Georgia

The Human Adrenal Cortex

A. R. CURRIE, T. SYMINGTON, and J. K. GRANT, editors, 1962. *Baltimore: Williams & Wilkins Co*. 644 pages. Illustrated. \$11.00.

This text consists of the proceedings of a conference held at the University of Glasgow, Scotland, in July 1960. Among the 93 contributors from both sides of the Atlantic, 3 are from the University of Minnesota.

The book is divided into 6 parts, with each part in many chapters. The main sections consist of discussions on morphology, biochemistry of the adrenocortical hormones, control of adrenocortical secretion, metabolic effects of adrenocortical hormones, diseases, and fetal adrenal cortex. Of special value is the inclusion of a chapter devoted to discussion and summary of each of these major areas.

Throughout the book, one is impressed by the concise and logical presentations. Illustrations and tables are of uniformly high quality and appropriate to the written material. Every paper has a complete up-to-date bibliography. As may be surmised from the main subdivisions, there is an excellent blending of the experimental and research aspects with the practical problems related to disease processes. There are several papers devoted to aldosteronism, one of which is a review.

The average student or physician may find this book to be more complete than he needs or has time for in a busy schedule. But for those who have a special interest in the adrenal gland, the volume is highly recommended as a complete, current, readable reference with excellent bibliography.

RICHARD P. LYNCH, M.D.
St. Paul

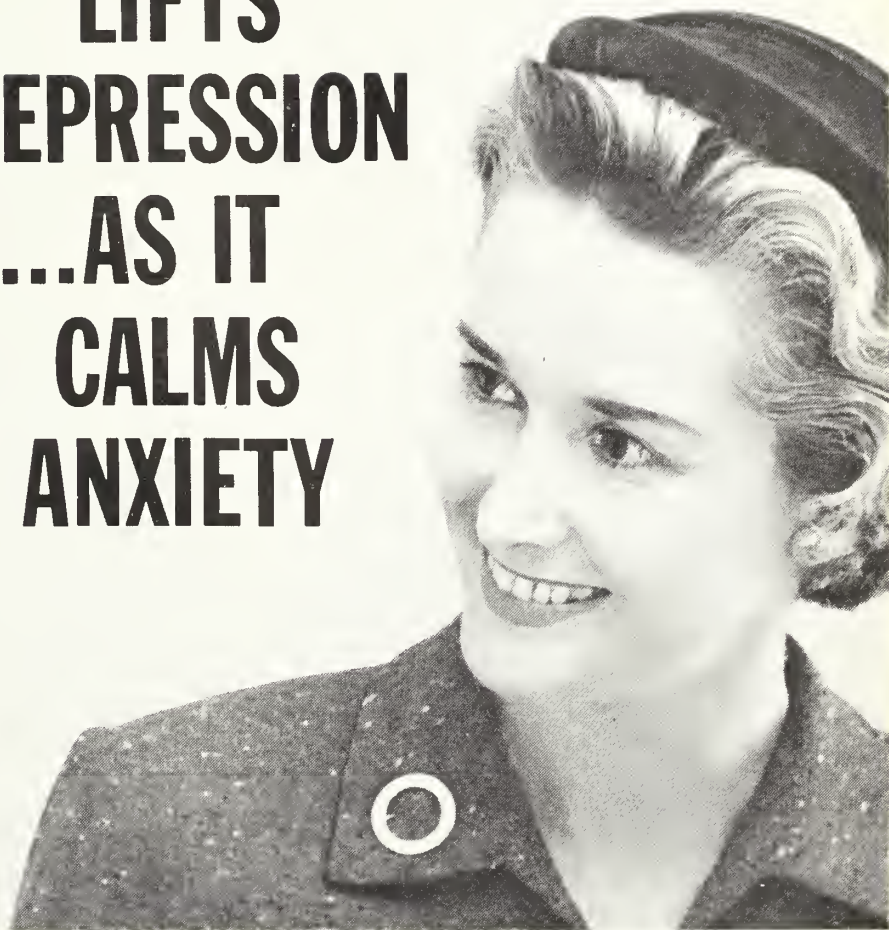
Symposium on Use of Indicator-Dilution Technics in the Study of the Circulation

EARL H. WOOD, M.D., editor, 1962. *New York: American Heart Association, Monograph No. 4*. 192 pages. Illustrated. \$2.50.

For the most part, this monograph is mathematical and technical, with the exception of 2 chapters. For those who are, let us say, purely clinically minded, these 2 chapters alone, "Diagnostic Applications of Indicator-Dilution Technics in Congenital Heart Disease" and "Speculations Concerning Present and Future Develop-

(Continued on page 16A)

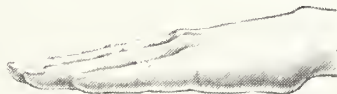
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BOOK REVIEWS

(Continued from page 406)

ments in Indicator-Dilution Technics," by Dr. Wood, make the book worth the nominal price charged by the American Heart Association. These chapters summarize previous publications by Dr. Wood in the field of indicator dilution technics. They are beautifully diagrammed, clear, and logical and present an excellent lesson in physiology and medicine in the cardiac field of acquired and congenital disease.

The contributing authors are experts in the field and although their presentations are for the most part mathematical, they will undoubtedly be a must to those who do investigative work in the field of indicator-dilution technics for the study of the circulation.

The book is recommended to physicians and physiologists. For medical students, physicians in general practice, cardiologists, cardiac surgeons and medical libraries, the book is essential.

ARTHUR M. MASTER, M.D.
New York City

Thannhauser's Textbook of Metabolism and Metabolic Disorders

NEPOMUK ZÖLLNER, M.D., *editor*. Translated by SOLOMON ESTREN, M.D., 1962. New York: Grune & Stratton. 462 pages. Illustrated. \$17.50.

This book, first published in 1929 and written entirely by Dr. S. J. Thannhauser, became one of the most widely read monographs on the biochemistry of metabolic disorders. Twenty-six years elapsed before the publication, in 1957, of a completely revised German edition. The second edition is divided into 2 volumes and is edited by Dr. Nepomuk Zöllner of the University of Munich, a former student and associate of Dr. Thannhauser. Fifteen authorities in metabolic research from Europe and the United States have written chapters. Dr. Thannhauser is not a contributor to the second edition and says in the preface that he wishes to turn the revision over to younger men who are specialists in the various areas of the greatly expanded field of metabolic research. The very excellent translation of Volume I into English is done by Dr. Solomon Estren of the Mount Sinai Hospital, New York, published in 1962.

This is not a textbook of endocrinology, as may be implied by the title. No attempt is made to cover the spectrum of clinical endocrine disorders and they are discussed only in their relation to disturbances in the biochemistry of metabolism. Volume I is concerned with current concepts and recent advances of knowledge in the fields of general and intermediate metabolism and the metabolism of carbohydrates, proteins, and amino acids. Throughout, a discussion of theoretic and basic biochemical considerations is followed by a presentation of clinical implications. Although much of the text is devoted to biochemistry, the authors have succeeded in presenting this material in a precise and clear manner, so that the reader is constantly made aware of the clinical significance of disturbances in metabolic biochemistry. There are excellent, comprehensive sections discussing the clinical aspects of obesity, malnutrition, thyroid dysfunction, avitaminosis-B disorders, and diabetes mellitus. The section on diabetes covers, in detail, pathogenesis, diagnosis, complications, and therapy, including the use of the different insulins and the oral insulinlike agents. Dr. Jan Waldenström has contributed an excellent chapter on clinical disorders of plasma pro-

teins and amino acids. The illustrations are well done and a very complete bibliography is included at the end of each chapter.

Volume I is a complete text in itself on the subjects covered. Volume II will deal with the metabolism of nucleic acid, mucopolysaccharides, lipids, steroids, blood and bile pigments, coagulation, iron, calcium, water, and electrolytes. I find little to criticize in this very well done book and recommend it to both clinicians and basic scientists as a valuable addition to their libraries, either to be read from cover to cover or to be used as a reference source.

ALVIN L. SCHULTZ, M.D.
Minneapolis

The Senior Citizen

RALPH BEATTY, M.D., F.A.C.S., 1962. Springfield, Ill.: Charles C Thomas. 180 pages. \$6.75.

This attractive volume from the files of a reporter-surgeon is an expanded collection of highlights selected chiefly from the author's weekly column in the *Uniontown Herald*, Uniontown, Pennsylvania. A prominent surgeon and specialist in urology, with a flair for writing and a responsiveness to the anecdote, Dr. Beatty is well equipped to assemble his impressions of the compensations and vexations which the aging citizen comes to know.

The book consists of 4 parts, the first of which includes a discussion on the process of aging and the impact of retirement. In this section, the author summarizes information available at the present time, with particular reference to preparation for retirement. His conclusions are in accord with those of the majority of students of the problem who recommend that retirement should be on a functional and capability basis rather than at a fixed age. This is a continually changing factor because of the advances of science, the benefits of which are maintaining many citizens in excellent health far beyond the three-score years and ten milestone. The author reviews a number of problems facing the older and emphasizes the necessity for recognition of motivation as a major influence in healthy living in the later years.

The physical and mental processes affecting the aged comprise the second part of the book, which includes a review of the impact of diseases on aging. The author outlines some timely hints taken from reports from the American Medical Association and, in addition, discusses a new concept of disease which he identifies as "biological predeterminism." In essence, this would seem to refer to the genetic endowment of an individual as predetermining his future. Comparing this concept with theological predestination in the religious field introduces an idea which might be difficult to support.

Part 3 deals with the essential housing and hospital needs and offers a discussion of finances with particular reference to the various kinds of insurance available. This is an excellent feature of the work and will be of interest to all older citizens.

In part 4, the author discusses the senior citizen as a public servant. He emphasizes the older person's value in the community and the necessity for accepting responsibility in social activities. Senior citizens have an opportunity to render valuable service as public servants, either as volunteers or as employees. In the latter part of this section, consideration of the religious interests and the importance of planning for the years ahead are emphasized.

While the author is not concerned with the basic

(Continued on page 18A)



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BOOK REVIEWS

(Continued from page 16A)

biologic and medical details, his informal approach, generously supported by illustrative cases, holds one's attention throughout.

The arrangement of the material might have been more logical. The traditional practice introduces fundamentals, then proceeds to details. However, the nature of the author's material permits a flexibility of sequence and progression which is acceptable.

The author's views are safely conservative and in accord with modern medical thinking. The busy physician will enjoy the folksy, homespun philosophy which flows through the chapters.

While there is nothing new for the professional man, this easy to read report should find generous acceptance by the public. Its hopeful spirit is exhilarating. The format adheres to the usual high standards of the Charles C Thomas Company. Attractively and clearly printed, it should have a wide distribution.

EDWARD L. BORTZ, M.D.
Philadelphia

Physiological and Pathological Ageing

V. KORENCHEVSKY, M.D., 1961. *New York: Hafner Publishing Company. 514 pages. Illustrated. \$22.50.*

In the science of gerontology, few names are as well known as is that of V. Korenchevsky. This may be partly a matter of seniority, since Dr. Korenchevsky was in the vanguard of medical scientists who have thought about and worked to solve the problems of aging. Nevertheless, the impact of his book is not based on the reputation of the author but on the valuable contribution it makes to the practice of geriatric medicine by providing a clear summary and interpretation of the results of many years of research in gerontology. Dr. Korenchevsky is particularly adept at this translation. His leadership of international research committees and of research in aging in Great Britain for the past twenty years has equipped him to speak authoritatively about the research basis of geriatric practice. The book was edited posthumously for Dr. Korenchevsky by Dr. Geoffrey Bourne, professor and chairman of anatomy at Emory University in Atlanta, Georgia.

The early chapters of the book briefly review the basic biology of aging and the final chapters contain brief discussions of geriatric treatment and over-all interpretations of results. Between these there is an extensive critical review arranged according to organs and organ systems. The emphasis of the review is on the endocrine glands (ch. X), the ovaries (ch. XI), and the other glands (chs. XII, XIII, XIV, XV, and XVI). Even the pineal (ch. XVIII) has a chapter to itself. Chapter IX contains an interesting and informative discussion of auto-intoxication, while chapters VII and VIII are well-documented reviews of chemical changes and metabolism. Those readers interested in the heart, kidneys, and nervous system will be disappointed that these topics were not treated more fully.

References dated as late as 1956 accompany most chapters. These include the Russian literature, which Dr. Korenchevsky was able to interpret effectively.

This book is recommended for physicians and medical scientists, not only because of the wealth of detail it contains but also because the reader cannot help but be influenced by Dr. Korenchevsky's philosophy of sound treatment based on sound research.

ARTHUR H. NORRIS
Baltimore

BOOK REVIEWS

NEW BOOKS RECEIVED

Books and publications received will be listed here periodically, and such mention must be regarded as sufficient return for the courtesy of the sender. Books of special interest to our readers will be reviewed as space permits.

An Introduction to the Study of Disease. WILLIAM BOYD, M.D., fifth edition, 1962. Philadelphia: Lea & Febiger. 478 pages. Illustrated. \$7.50.

Ciba Foundation Symposium on Tumour Viruses of Murine Origin. G. E. W. WOLSTENHOLME and MAEVE O'CONNOR, editors, 1962. Boston: Little, Brown & Co. 441 pages. Illustrated. \$10.75.

Muscle as a Tissue. KAARE RODAHL, M.D., and STEVEN M. HORVATH, PH.D., editors, 1962. New York: McGraw-Hill. 331 pages. Illustrated. \$15.00.

Medical Genetics 1958-1960. VICTOR A. MC KUSICK, M.D., 1961. St. Louis: C. V. Mosby Co. 534 pages. Illustrated. \$14.50.

Mental Retardation. Proceedings of the Association for Research in Nervous and Mental Disease, December 11 and 12, 1959, New York. LAWRENCE C. KOLB, M.D., RICHARD L. MASLAND, M.D., and ROBERT E. COOKE, M.D., editors, 1962. Baltimore: Williams & Wilkins. 331 pages. Illustrated. \$15.00.

The Year Book of Drug Therapy, 1961-1962 Series. HARRY BECKMAN, M.D., editor, 1962. Chicago: Year Book Medical Publishers. 597 pages. Illustrated. \$8.50.

The Mechanism of Action of Water-Soluble Vitamins. A. V. S. DE REUCK, and MAEVE O'CONNOR, editors, 1961. Boston: Little, Brown & Co. 120 pages. Illustrated. \$2.50.

The Pluricausal Cardiopathies. HANS SELYE, 1961. Springfield, Ill.: Charles C Thomas. 438 pages. Illustrated. \$21.00.

Medical Pharmacology: Principles and Concepts. ANDRES GOTH, M.D., 1961. St. Louis: C. V. Mosby Co. 551 pages. Illustrated. \$11.00.

Clinics in Electrocardiography. DALE GROOM, M.D., 1960. Springfield, Ill.: Charles C Thomas. 152 pages. Illustrated. \$8.00.

Science and Psychoanalysis. Volume V: Psychoanalytic Education. JULES H. MASSERMAN, M.D., editor, 1962. New York: Grune & Stratton. 332 pages. \$9.75.

Evaluation of the Toxicity of a Number of Antimicrobials and Antioxidants. WORLD HEALTH ORGANIZATION, 1962. Geneva, Switzerland: World Health Organization. 104 pages. \$1.25.

Proceedings of the Conference on Genetic Polymorphisms and Geographic Variations in Disease. BARUCH S. BLUMBERG, 1962. New York: Grune & Stratton. 229 pages. Illustrated. \$5.75.

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News Briefs . . .

North Dakota

DR. PAUL RETZER has become associated with the Hettinger Clinic. He received his medical degree from the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina and recently completed internship at St. Luke's Hospital in Fargo.

DRS. RUSSELL O. SAXVIK, Roger W. Fricke, and Gerd Fischer have become members of the Quain and Ramstad Clinic in Bismarck. Dr. Saxvik, former superintendent of the State Hospital in Jamestown, will establish a department of psychiatry at the clinic. Dr. Fricke is a specialist in internal medicine, and recently completed his residency at Saginaw General Hospital in Michigan. Dr. Fischer, a specialist in neurosurgery, will establish a department of neurosurgery at the clinic.

DR. DELBERT HLAVINKA, a native of Grant County, has joined Drs. Melvin S. Jacobson, J. M. Bahamonde, and A. A. Curiskis of the Elgin Clinic. Dr. Hlavinka received his medical education from the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.

DR. GEORGE A. SKELLY, a native of Winnipeg, Manitoba, has begun practice in Cooperstown. Dr. Skelly, a Canadian infantry officer for six years, took up the practice of Dr. Lars Vistnes, who has moved to San Francisco.

DR. ROBERT FORTUINE, a graduate of McGill University Faculty of Medicine, Montreal, Quebec, has become the medical officer in charge of the Public Health Service Indian Hospital in Belcourt. He relieves Dr. Thomas K. Huggins, who left Belcourt to begin private practice in Galion, Ohio, after completing a two-year tour of duty. Dr. Fortune has served on the hospital staff for a year.

DR. RICHARD F. RAASCH, a member of the medical staff of St. Joseph's Hospital in Dickinson, has become president of the North Dakota Radiological Society.

DR. BERCHMANS J. RIOUX, former director of the receiving and treatment center of the State Hospital in Jamestown, plans to begin private practice in Minot. Dr. Rionx is a native of Quebec, Canada.

DR. CHARLES A. ARNESON, Bismarck surgeon and colonel in the Army Reserve, has a new reserve assignment as deputy surgeon of the Fifth Army, headquarters in Chicago. Dr. Ralph E. Mahowald of Grand Forks replaces Dr. Arneson as commander of the 311th General Hospital unit. Dr. Arneson is continuing private practice in Bismarck.

DR. JAMES H. COFFEY has joined the department of pathology of the Fargo Clinic and has become associated with Dr. John D. LeMar. Dr. Coffey is a native of Omaha, Nebraska. He received his medical degree from the University of Nebraska College of Medicine, Omaha.

DR. THOMAS L. SUSSEX has moved from Watford City to Minot where he is associated with the Great Plains Clinic. While living in Watford City, he served as the McKenzie County Health Officer.

A TOTAL OF 25 DOCTORS have been licensed by the North Dakota Board of Medical Examiners. Doctors licensed by reciprocity and the locations where they will practice are John B. Frankel, Bismarck; James B. Wenzel, Fargo; James H. Coffey, Fargo; Richard H. Seifert, Fargo; Howard R. Gray, Bismarck; John A. Lambie, Grand Forks; John W. Miller, Fargo; Duane D. Rubbert, LaMoure; and John F. Leonard, serving in the Air Force at Minot. Doctors licensed by examination and the locations of their practice are T. F. Gibson, surgeon and internist, and his wife, Shelagh Milligan, pediatrician and anesthesiologist, of Gainsborough, Saskatchewan, practicing in Mohall; Delbert Hlavinka of Lark, Elgin; Paul Retzer of Zap, Hettinger; Myron D. Peterson of Norwich, Minot; Roger W. Fricke of Baldwin, Bismarck; Donald J. Breen of Hillsboro who is in the Air Force; William F. Hook of Bismarck with the Navy; George A. Skelly of St. Boniface, Manitoba, Cooperstown; R. Natarajan of India, Grand Forks; Mehmet H. Nazli of Turkey, Minot. Licensed by examination but undecided as to where they will practice are T. M. Black, obstetrician and gynecologist, from Regina, Saskatchewan; F. B. Webber of Bienfait, Saskatchewan; Amedee P. Isabey of Boniface, Manitoba; Helmut Arnold of Germany; and Roland Fleck of Innsbruck, Austria.

THE NORTH DAKOTA SOCIETY OF OBSTETRICS AND GYNECOLOGY fall meeting will be at the Town House, Fargo, September 14 and 15. Guest speakers will include Drs. Lowell Peterson of Chicago, Charles Hendricks of Cleveland, and Laman Gray of Louisville. Papers to be presented by Dr. Peterson are entitled (1) Gynecological Considerations in the Preadolescent and the Adolescent Female and (2) Geriatric Gynecology; by Hendricks, (1) Induction of Labor and (2) Premature Birth; and by Dr. Gray, (1) Carcinoma of the Ovary; Histogenesis and Clinical Findings, and (2) Treatment of Vaginitis with Special Reference to Flagyl. Dr. Peterson also will show a movie on examining adolescent and preadolescent girls. Dr. John Moore of Grand Forks will present a report from the State Maternal Mortality Committee. Dr. C. A. Johnson will speak after dinner, and evening entertainment will be provided by the Dixieland Jazz Band of Doe Evans.

Minnesota

DR. RICHARD P. PAYNE plans to return to the East Range Clinic in Virginia after spending over half a year at the African Lutheran mission station in Garoua-Boulai, Cameroun. Dr. Payne found the natives receptive to medical care.

DR. DONALD B. PETERSON has resigned as superintendent of the Anoka State Hospital, attacking the state welfare department's administrative policy of installing non-

(Continued on page 22A)

Introduction to Special Issue on Pediatric Hematology

THE art of healing remains as "the core" of medical practice. The magic of a doctor is to turn the bleak tide of events into a whole and happy outcome. Such effective therapeutic measures are dramatically presented in Dr. Hodapp's paper on the difficulty of treating hypertransfused hypervolemic infants. Dr. Lowman's discussion of therapy of acquired hemolytic anemia and Dr. Steiger's use of epsilon-aminocaproic acid as part of hemophilia therapy are all portions of a therapeutic endeavor needed to restore health.

Yet, in pediatrics the ounce of prevention assuredly looms larger in final benefits compared with the pound of cure. Preventive measures against death and disease are presented in great detail in this pediatric hematology issue. The presence of kernicterus, a clearly preventable disease, deserves attention and thoughts of all physicians. Dr. Fisch's report on the occurrence of kernicterus is both quite startling and practical. Drs. Quie, Fisch, and Raile report on production of methemoglobinemia, anemia, and hemolysis in the newborn as a result of exogenous material in neonatal nursery. Dr. White addresses himself to the problem of how to be suspicious of a coagulation disorder on historic data alone. Knowing that a patient has a coagulation disorder can prevent and minimize damage.

Laboratory studies form the background of our diagnostic ability and are presented by Dr. Yunis on ABO hemolytic disease, by Dr. Clawson on melena neonatorum, and by Dr. Kozak on modern concepts of spleen and anemia. A review of causes of neutropenia is provided by Dr. Page.

In short, this issue is provided for the physician's intelligent appraisal of the advances and pitfalls present in pediatric hematology.

WILLIAM KRIVIT, M.D.
Guest editor

The Importance of History in the Diagnosis of Congenital Coagulation Disorders

JAMES G. WHITE, M.D.

Minneapolis

ACCURATE historic review for bleeding signs and symptoms remains the most important criterion in the diagnosis of congenital bleeding syndromes. Despite the plethora of laboratory tests, no procedure has been developed which can replace the carefully elicited history.^{1,2} The methods of historic inquiry are not difficult. When utilized, they enable any physician to detect congenital coagulation disorders.

The importance of the history will be demonstrated in this paper by case presentation. Questions in the history which will detect abnormal bleeding will be emphasized.

VITAMIN K ANACHRONISM

Case 1. This 10-year-old boy is presented as an example of the complications which may follow dental extraction when the family physician and dentist fail to utilize the history as a diagnostic test.

When the patient was 9 years old he underwent dental extraction. He was hospitalized for three days after this procedure in order to control excessive postoperative bleeding. The hemorrhage was felt to be related to the trauma of the procedure and not to an intrinsic defect in coagulation. Six months later, a second tooth was extracted after preoperative injection of vitamin K. This second procedure was accompanied by considerable bleeding after surgery. Hospitalization was again required to control hemorrhage. Only after referral to another institution for a different medical problem was a historic review undertaken which made this child's problem apparent.

The child had been noted to bruise easily after slight trauma since beginning to walk at a year of age. He had frequent epistaxis which was difficult to control. On 2 occasions he had been hospitalized for uncontrollable nasal hemorrhage.

The mother of the patient had bruised easily all of her life. She had hemorrhaged after each delivery and after an appendectomy. Three of the child's 5 siblings were noted to bruise easily. Two brothers had prolonged bleeding after tonsillectomy and adenoidectomy (figure 1).

When this information had been obtained, the child was immediately referred for laboratory evaluation. The results of his clotting study indicated that he is a hemo-

philiac, deficient in plasma thromboplastin antecedent (P.T.A.).

Comments on case 1. The preoperative use of vitamin K in this patient indicates a significant failure to comprehend the nature of a bleeding problem. Vitamin K deficiency is exceedingly rare as a cause of abnormal bleeding and is never found in the otherwise healthy child.³ One who uses this drug when abnormal bleeding is anticipated ignores the lessons learned over the years and places the patient's life in jeopardy. The routine preoperative use of vitamin K in the healthy child undergoing elective surgery is never indicated. One cannot rely upon drug therapy to replace the simple method of taking a history.

Recurrent nasal hemorrhage may not in itself suggest abnormal hemostasis, but when other bleeding signs easily elicited by a few questions are evident, laboratory evaluation is imperative. Schulman⁴ described 22 children with epistaxis as the only sign of unusual bleeding and compared them with 22 children in whom recurrent nosebleed was accompanied by some other sign of easy bleeding. Laboratory evaluation failed to detect any abnormality in the first group; however, in the second group, 21 of the 22 patients with associated manifestations of abnormal bleeding had laboratory evidence of defective hemostasis.

If the family history of this child and his personal history of lifelong difficulty with easy bleeding had been sought before surgery, the danger of prolonged bleeding after dental extraction could have been appreciated. The use of vitamin K as a routine preoperative hemostatic under these circumstances can only be condemned.

HISTORIC PARADOX

Case 2. Two weeks prior to admission at this hospital, a 3-year-old boy developed a lump on the left side of his head. This swelling continued, and the child was admitted to a local hospital. The large swelling was recognized as a hematoma, and needle aspiration was performed unsuccessfully in order to control progression. Skull roentgenograms and bilateral carotid angiograms

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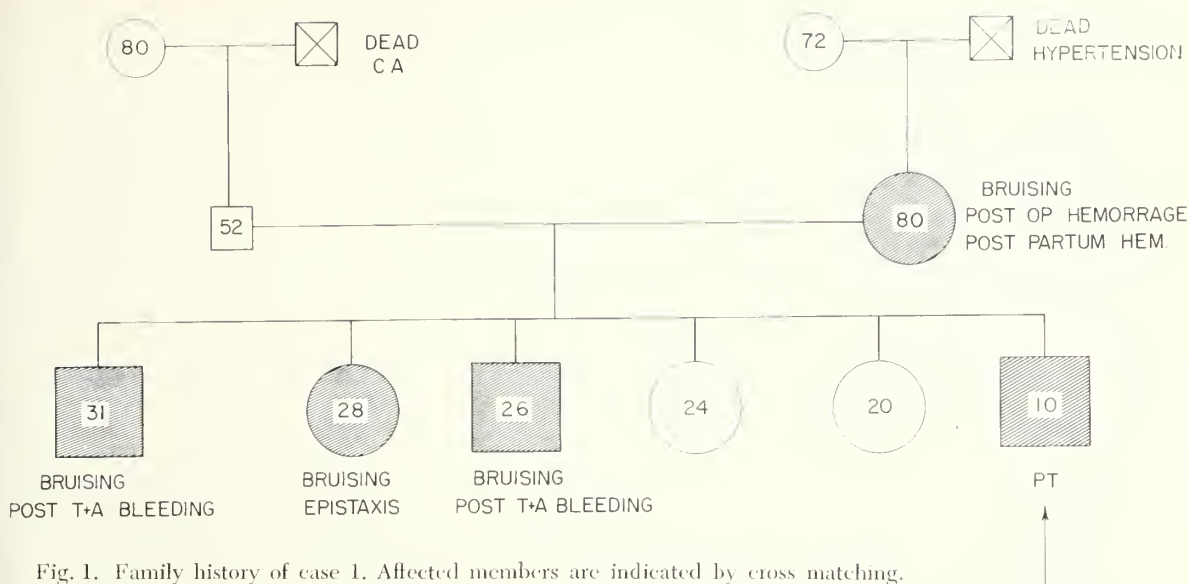


Fig. 1. Family history of case 1. Affected members are indicated by cross matching.

were obtained and were negative. In view of the continued enlargement of the hematoma, surgery was decided upon. The scalp was widely incised and a skin flap was turned. The hematoma was evacuated, and a careful and extensive search for a bleeding point was made. The surgical field was felt to be dry at the time of closure. Despite this effort, the hematoma rapidly reaccumulated, requiring frequent blood transfusions. The child's condition did not improve, and he was transferred to the University Hospitals. His head was twice normal size at the time of admission.

A perusal of the child's medical history was most revealing. He had been noted to develop hematoma out of proportion to the degree of trauma since infancy (figure 2). At a year of age, a hemangioma had been noted on his tongue. Because of bleeding from this lesion at the time of recognition, cauterization was attempted. Bleeding persisted, however, and the child was hospitalized. Seven surgical procedures and a number of transfusions were required before the bleeding was controlled.

The child's maternal grandfather was known to bleed easily and excessively, particularly following dental extractions. The mother of the patient bled excessively after a thyroidectomy and gynecologic surgery. She had also noted easy bruising all of her life. In another institution, a male cousin of the patient had been diagnosed as a hemophilic deficient in antihemophilic globulin (A.H.G.).

On several occasions, the parents of the patient had queried the child's physician concerning his bleeding problem. Routine clotting studies were performed and proved normal. These results and the fact that he did not bleed excessively from small cuts were false reassurance that no bleeding problem existed in this child.

Laboratory investigation after transfer was diagnostic of a coagulation deficiency in antihemophilic globulin. Continuous infusion of fresh-frozen plasma and fresh blood ultimately restored the deficit in the clotting mechanism and hemoglobin. The hematoma gradually responded to medical management.

Comment on case 2. Total reliance upon so-called routine clotting studies, in this case the

bleeding time and clotting time, is to be condemned. Diamond and Porter,^{1,2} Aggeler and co-workers,³ Fletcher,⁴ and others^{3,7-9} have stressed that these routine tests of bleeding and clotting will provide a false sense of security since they do not detect patients with congenital coagulation disorders. Table 1 suggests the frequency with which normal clotting times may be observed in various forms of hemophilia.

When the history suggests a bleeding problem, there is no hemorrhagic disorder which



Fig. 2. A hematoma which occurred after mild trauma in case 2 at 2 years of age. Note the size of the hematoma by comparing the 2 sides of his face. This boy had a massive football-size hematoma develop following surgical trauma at a later date.

TABLE 1
FREQUENCY OF NORMAL CLOTTING TIMES
IN PATIENTS WITH VARIOUS TYPES OF HEMOPHILIA⁵

<i>Type of hemophilia</i>	<i>Normal clotting time</i>		<i>Prolonged clotting time</i>	
	<i>Number</i>	<i>Per cent</i>	<i>Number</i>	<i>Per cent</i>
A—Antihemophilic globulin (A.H.G.)	37	35	68	65
B—Plasma thromboplastin component (P.T.C.)	20	59	14	41
C—Plasma thromboplastin antecedent (P.T.A.)	10	100	0	0

must not be considered.⁷ Therefore, a complete study of the capacity for hemostasis involving evaluation of the 3 phases of coagulation, platelet numbers, and platelet function must be performed. Infrequently the results of such testing may be normal despite a suggestive history. This does not mean that the patient does not have a bleeding disorder; it merely indicates the need for reevaluation of the history and repeated laboratory testing. The history has a higher index of reliability than any laboratory procedure.

The drainage of hematomas in hemophilic patients because of their size or persistence should never be done. The normal mechanism of fibrinolysis is eminently capable of removing any accumulation of blood if normal coagulation can be maintained. If these systems are defective, treatment by incision will only induce further bleeding or introduce infection.

The failure to recognize the significance of the history compounded a difficult clinical situation. The sequence of events which followed this error demonstrates succinctly the paradox that can arise when the history is deferred in favor of laboratory studies.

DISCUSSION

A bleeding tendency must be suspected in every patient and sought after by careful inquiry. The detection of abnormal bleeding states is not difficult. Diamond¹ has reported that he has yet to see a patient with a congenital disorder who did not have a significant history by the time he reached 2 years of age, no matter how mild the disease.

In most hemophilic patients with severe clotting factor deficiencies, the history will be marked by frequent episodes of hemarthrosis, hematuria, gastrointestinal bleeding, and intra-abdominal and retroperitoneal hemorrhage.¹⁰ The family history will demonstrate a degree of severity of bleeding in relatives comparable to that observed in the patients themselves.¹¹⁻¹³ Yet, it should be noted that 25 per cent of patients with hemophilia will be unaware of a bleeding problem in any other member of their

family.⁷ The failure to elicit evidence of a familial bleeding tendency does not exclude the possibility of inherited disease. The clotting abnormality may not be expressed for several generations or it may be so mild as to go unnoticed, or both.¹⁴

In the moderate or occult hemophilias, the problem of obtaining relevant history is more difficult. Although the incidence of hemophilia does not appear to be increasing, the relative number of patients with moderate hemophilia is becoming proportionately greater, emphasizing the importance of seeking evidence of abnormal hemostasis.⁶ This is particularly true in

TABLE 2
SIGNS OF DEFECTIVE HEMOSTASIS

- A. Spontaneous bleeding
 1. Epistaxis (associated with other evidence of easy bleeding)
 2. Cutaneous bleeding (petechia, ecchymosis, hematoma)
 3. Oozing from mucous membranes or gums
 4. Menorrhagia
 5. Postpartum hemorrhage
- B. Bleeding in unusual sites
 1. Central nervous system bleeding
 2. Genitourinary tract bleeding
 3. Gastrointestinal tract bleeding
 4. Retroperitoneal hemorrhage
 5. Bleeding into muscles
 6. Bleeding into joints
 7. Bleeding accompanying eruption of deciduous teeth
- C. Postsurgical bleeding (prolonged)
 1. Circumcision
 2. Tonsillectomy and adenoidectomy
 3. Dental extraction
 4. Incision and drainage
 5. Cutdown
 6. Venesection (followed by ecchymoses or hematoma)
- D. Trauma followed by bleeding out of proportion to the degree of injury
 1. Minor lacerations (copious or persistent bleeding)
 2. Hematoma and ecchymosis (recurrent and protracted)
 3. Easy bruising in protected areas (buttocks, back)
- E. Bleeding from multiple sites simultaneously

the patient whose mild bleeding symptoms have become an accepted part of daily life and, therefore, are not considered by him to be abnormal. Direct questioning is essential to reveal their presence.

A consideration of examples of abnormal hemostatic response will detect the bleeding states (see table 2). Trauma is a normal daily occurrence during the growth and development of every individual. From birth onward these tests of trauma provide a convenient means of assessing the presence of a bleeding disease.¹⁵

Circumcision followed by a continued loss of blood will occur in 30 per cent of the children with classic hemophilia.¹⁰ If an easily clamped vessel is not immediately apparent as the cause of the bleeding, a hemorrhagic disorder is indicated until proved otherwise. Bumping against the sides of the crib is difficult to prevent in the child over 6 months of age. This mild trauma seldom produces hematomas in the normal child. If hematomas do develop as a result of this misadventure, then a hemorrhagic state must be considered. Epistaxis in the normal infant is also uncommon. This sign, if isolated in the older child, does not indicate abnormal bleeding,^{4,12} but it certainly does so in the infant age group. Immunization injections, needle pricks for blood tests, or small lacerations followed by profuse or prolonged bleeding, or the formation of hematomas suggest a hemorrhagic disorder. Bleeding after mild trauma from multiple sites simultaneously or into unusual areas, such as the central nervous system and intra-abdominal or retroperitoneal sites, should immediately arouse suspicion of an inadequate hemostatic mechanism.¹ The bumps and bruises sustained by the normal child as he learns to walk and run should not involve large areas of an extremity or the entire side of his head. Such hematomas are obviously out of proportion to the degree of trauma inducing them. In addition, these accumulations of blood should resolve spontaneously with evidence of resorption, such as softening, discoloration of the skin, and lessening of the pain within twenty-four hours after appearance.

Genitourinary or gastrointestinal hemorrhage and hemarthroses are always abnormal and always require consideration of disordered hemostasis. Excessive or prolonged bleeding following the frequently performed operations of childhood is the most common presenting complaint of patients with mild hemophilia.⁵ The amount and duration of bleeding following dental extraction depends upon the size of the tooth removed and whether an incision was made to facilitate extraction. However, any continued

flow of blood from the tooth socket after surgery or any persistent ooze beyond the second day suggests a hemorrhagic disease.¹⁶ Difficulty in hemostasis immediately following tonsillectomy and adenoidectomy is far more significant than bleeding seven to ten days postoperatively as the clot is sloughed.¹¹ Any persistent flow of blood or build-up of clot after this procedure is abnormal.¹⁵ One must be careful to recognize that blood may be dripping from the tip of a clot hanging in the hypopharynx and may not be readily visible through the mouth. The presence of the clot does not mean that hemostasis has been achieved.

The presence of bleeding due to one of the causes previously cited may not in itself warrant concern if the symptoms are moderate. However, persistent failure to pass these tests of trauma indicates the presence of a hemorrhagic state and demands investigation. There are a variety of other factors that test the intact hemostatic mechanism. They are not included in this description, but a careful perusal of those described in each patient will detect congenital bleeding syndromes.

As noted before, the family history is particularly useful in establishing the inherited nature of a bleeding disease. Since over 90 per cent of all congenital deficiencies of clotting factors will be either hemophilia A (antihemophilic globulin) or hemophilia B (plasma thromboplastin component), a sex-linked mode of inheritance should be sought.¹⁰ The presence of bleeding symptoms in the carriers should also be recognized. The frequent complaints of mild bleeding symptoms by mothers of hemophilic children were ignored until testing methods became sensitive enough to demonstrate moderate clotting factor deficiencies in the heterozygous state.¹⁷

If there is no indication of a familial bleeding tendency, an acquired bleeding syndrome must be considered. The bleeding, although symptoms may persist for years, does not go back to infancy, and the hemorrhagic manifestations are usually associated with an underlying disease or some precipitating cause.¹¹

SUMMARY

1. Every medical history should include a careful estimate of the patient's capacity for hemostasis.

2. The complications which may ensue when this maxim is ignored are demonstrated by the 2 patients presented.

3. Historic tests of trauma, which will be of aid in detecting abnormal bleeding states, are detailed. When suspicion is aroused, careful

exploration of other areas of the history, including age of onset, duration of symptoms, bleeding pattern, and family history, will often suggest the nature of the disorder.

4. At the present time there are no routine studies of hemostasis capable of replacing the carefully elicited history.

We wish to acknowledge the following granting agencies for their support in making these studies possible: United States Public Health Service (H-3107) (H-5341) (AM-02917-04) and Minnesota Division, American Cancer Society.

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CONCURRENT OR SUCCESSIVE acquired hemolytic anemia and thrombocytopenic purpura, due to underlying disease in about three-fourths of patients, may infrequently be signs of Evans' syndrome, an autoimmune phenomenon affecting red cells and platelets. Diagnosis of the Evans' syndrome is based on (1) remissions and exacerbations of primary acquired hemolytic anemia and thrombocytopenic purpura, (2) demonstrable immune mechanisms, (3) positive Coombs' test reaction, and (4) lack of secondary etiologic factors. Prognosis is guarded, but prolonged survival is occasionally seen. Adrenal steroids treatment, blood transfusion, and splenectomy may be beneficial. The cause of the primary hematologic defects is idiopathic in the lack of demonstrable immune mechanisms. More common causes of secondary acquired hemolytic anemia and thrombocytopenic purpura, with or without demonstrable immune mechanisms, include drug administration; infection; liver, collagen, or renal disease; sarcoidosis; and hematologic conditions such as leukemia, lymphoma, thrombotic thrombocytopenic purpura, and congestive splenomegaly.

During 1950-58, 25 patients with acquired hemolytic anemia and thrombocytopenic purpura were seen; 6 had Evans' syndrome, 8 lymphoma or leukemia, 5 cirrhosis, 2 thrombotic thrombocytopenic purpura, 2 chronic nephritis, 1 tuberculosis, and 1 lupus erythematosus.

Only 1 of the patients with Evans' syndrome had a palpable spleen. A total of 4 patients had splenectomy, but only 1 had prolonged benefit. Of the 6 patients, 4 have died.

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The Case of the Red and White Minnesota Twins

Intrauterine Blood Transfer Between Twins

ROBERT V. HODAPP, M.D.

Willmar, Minnesota

IN 1942, Herlitz¹ first described the simultaneous occurrence of anemia and polycythemia in a pair of newborn monozygotic twins. Since then, 17 such cases have been reported.¹⁻⁸ The purpose of the present report is to add another case to the accumulated literature. This seems worthwhile because, in severe cases, both the anemic and the polycythemic twin may need prompt treatment.

CASE REPORT

The mother, a 34-year-old, gravida VI, white female, delivered twin boys on December 28, 1961 (figure 1). She was approximately three weeks past her expected date of confinement. Her prenatal course had been uneventful. The labor was approximately six hours long. The first twin (A) was a cephalic presentation. The baby breathed spontaneously immediately after birth. He was noticeably pale. Weight was 5 lb., 8 oz. (2500 gm.). The second twin (B) delivered as a breech just four minutes after the first. He was somewhat slow in initiating respirations but did breathe spontaneously after about one minute. He was given oxygen inhalations by mask briefly and then breathed and cried well. Weight was 5 lb. (2270 gm.). The second twin was noticed to be a reddish-blue color at birth and had a suffused, plethoric look. The skin appeared to be stretched tight and was cracked and peeling. The heart and lungs were normal. There was no enlargement of the liver or spleen.

The placenta was inspected by the obstetrician and found to be a single ovum, monochorionic, and diamniotic. There did not appear to be any abnormal vessel communications in the placenta. No further tests or studies were done on the placenta which had been destroyed by the time the diagnosis of the hematologic abnormality in the twins was suspected.

Both twins did well during the immediate neonatal period. At approximately 12 hours of age blood counts were checked on capillary blood with the following results. Twin A: hemoglobin, 14.4 gm. per 100 cc., and white blood count, 13,800 with 87 per cent polymorphonuclear leukocytes and 13 per cent lymphocytes. Twin B: hemoglobin, 26.0 gm. per 100 cc.; and white blood count, 8,150 with 81 per cent polymorphonuclear leukocytes and 19 per cent lymphocytes.

The mother's blood type was B, Rh (D) positive. Both twins were type O, Rh (D) positive.

At 36 hours of age the hemoglobins were rechecked and microhematocrit determinations were as follows. Twin A: hemoglobin, 14.4 gm. per 100 cc., and hematocrit, 45 per cent. Twin B: hemoglobin, 28 gm. per 100 cc., and hematocrit, 83 per cent.

Twin A's hemoglobin stayed constant and his condition remained good. He was discharged from the hospital with the mother at 5 days of age.

Twin B's general condition was good, but because of concern for the possible consequences of the hemoconcentration and high viscosity of the blood it was elected to do a phlebotomy at approximately 44 hours of age. This was done using a polyethylene catheter in the umbilical vein. The venous pressure was measured and found to be 8 cm. of blood; however, because of the high viscosity of the blood, the measurement was felt to be an estimate. Forty cc. of blood was removed slowly. The baby tolerated the procedure well.

About sixteen hours after the phlebotomy, at age 60 hours, the baby started having respiratory difficulties, with grunting respirations and sternal retractions. He also vomited his glucose water feedings. A chest roentgenogram showed no cardiomegaly or gross pulmonary congestion. The liver and spleen were not enlarged. The pulse rate was 130 to 140 per minute, and respiratory rate was 36 to 40 per minute. Labora-

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Fig. 1. Color print of twins born December 28, 1961. Twin A (right) weighed 5 lb. 8 oz., and twin B weighed 5 lb.

tory work showed the hemoglobin to be 26.2 gm. per 100 cc. and the hematocrit 82 per cent.

Because of the respiratory and gastrointestinal difficulties, it was decided to stop oral feedings and to give the baby maintenance fluid and electrolyte requirements by way of an ankle vein cut-down. The baby was also digitalized with intramuscular digoxin, placed in a 35 per cent oxygen, high humidity atmosphere, and given therapeutic doses of intramuscular penicillin and chloramphenicol (Chloromycetin). These supportive and therapeutic measures were discontinued during the following week as the baby's condition improved.

Also during the first ten days of life, a total of 101 cc. of blood was removed by phlebotomy and venipuncture. The details of the blood withdrawal, hematologic values, and clinical data for Twin B are shown in figure 2.

There was no clinical evidence of jaundice at any time during the hospital stay.

Twin B was discharged from the hospital on January 14, 1962, at the age of 17 days. At the time of discharge the hemoglobin was 17.7 gm. per 100 cc. and the hematocrit was 54 per cent.

At 1 month of age I saw the baby in my office. At that time, physical examination was normal. Hemoglobin was 10.4 gm. per 100 cc. In retro-

spect it would seem that we were somewhat overzealous in removing blood from the baby. Both twins are now being treated with an oral iron preparation for their blood loss anemias, and both are doing well.

DISCUSSION

The mechanism for this unequal distribution of blood between the twins is not completely understood. It is well known that there are many anastomoses between the placental circulations of identical twins.⁹⁻¹¹ In his case, Bergstedt⁴ devised a "milk test" in which he injected milk into one of the cords. This resulted in both halves of the placenta becoming filled with milk. Klingberg and associates³ also demonstrated arteriovenous shunts between the placental circulations by perfusion of an artery in each cord with contrasting colored fluids. The mere presence of these communications does not explain the unequal distribution of blood. If the polycythemic twin is the second born, the possibility exists that more complete uterine contractions might force more placental blood into it or that an increased amount of blood might come from the placenta after the first cord is clamped. However, the polycythemic twin has been the first born in about half of the reported cases.

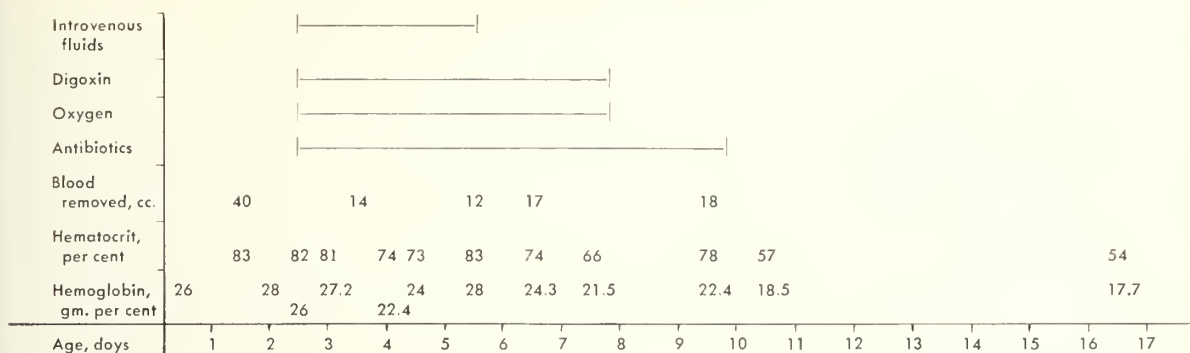


Fig. 2. Blood and clinical data for twin B

Also, the anemia of the other twin cannot be explained on this basis. In only 1 case has there been a rupture or tearing of the cord vessels which might account for the anemia in one of the twins.

Another postulation is that there must be some obstruction to the return of blood from the plethoric infant or obstruction to the entry of blood in the anemic one. This would agree with the placental findings which several authors have described—namely, engorgement of the placenta of the anemic twin and absence of engorgement of the placenta of the polycythemic one. In effect this would cause the polycythemic twin to be transfused by the anemic one. If this condition exists for some time before birth, it would also explain the evidences of hematologic hyperactivity characterized by reticulocytosis and erythroblastosis which have been reported in the anemic twin. The nature of this obstruction is difficult to determine. External pressure on one of the cords or on a superficial placental vessel by the growing fetuses themselves could produce the condition. There has been no proof of this, however, and it would be difficult to obtain. Perhaps closer study of the placentas will show some type of obstructive vascular abnormality.

In cases of intrauterine fetal-to-fetal transfusion there is a risk to both babies. In the 17 reported cases there have been 2 deaths among anemic twins and 1 death from residual cerebral palsy. The cause of death in both was prematurity. The anemic twin has a low hemoglobin concentration and possibly hypovolemia if the blood loss has been acute and has occurred shortly before delivery. This may require emergency treatment by transfusion. Neligan and Russell,¹² discussing fetal anemia due to blood loss after incision of the placenta during cesarean section, maintain that the exsanguinated baby may appear deceptively well until shortly before death. They suggest that a transfusion is

required if the peripheral blood hemoglobin level falls below 13.3 gm. per 100 cc. in the first twenty-four hours of life. Perhaps this level may also be taken as a guide in this type of case. Several of these anemic infants have been treated by multiple small transfusions or by direct transfusion of blood from the polycythemic twin.

Among polycythemic twins there have been 6 deaths. The causes of death were cerebral hemorrhage, kernicterus, atelectasis, bronchopneumonia, and prematurity. It would seem that the plethoric infant runs the greater risk.

The polycythemic infant is subjected to the possible hazards of hemorrhage, venous thromboses, pulmonary edema, and hyperbilirubinemia. Sacks⁷ suggests that the polycythemic twin should be bled slowly over a period of hours or days until the concentration of hemoglobin and the hematocrit readings reach a reasonable level. If the concentration of hemoglobin and the hematocrit readings are very high, it may be necessary to replace some of the circulating blood volume with plasma to obtain an adequate lowering of the packed cell volume within a reasonable time.

The infant should also be watched closely for jaundice, and serum bilirubin levels should be checked if indicated. The usual indications for the treatment of hyperbilirubinemia probably should be observed.

Other causes of polycythemia in the newborn infant are congenital adrenal hyperplasia,¹³ maternal-fetal transfusion,^{14,15} and possibly stripping of the umbilical cord at birth.¹⁶ The condition may also be secondary to cardiopulmonary disease and cyanosis or to dehydration with decrease in plasma volume. It is not within the scope of this paper to discuss these related problems but merely to mention them.

SUMMARY

A case of fetal-to-fetal transfusion in identical twins has been presented. This phenomenon re-

sulted in anemia of one of the twins and polycythemia in the other. The possible causes of this condition and some of the aspects of management have been discussed. It is hoped that the presentation of this case will stimulate practicing physicians to be alert to the diagnosis and the potential hazards of this situation.

The author wishes to thank Dr. Walter E. Hinz (Lake-land Medical Center, Willmar, Minnesota), who delivered these babies, for his help and cooperation, and Dr. William Krivit for his long distance telephone advice on the management of the hematologic problem.

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CINEFLUOROGRAPHIC EXAMINATION is the best means of detecting and recording epicardial fat lines within the cardiac silhouette. Pericardial effusion is indicated by decreased amplitude of pulsation of the pleuropericardial border, prominent fat lines about the heart, and increased distance between fat line and pleuropericardial border. Effusion is probable if the apical epicardial fat is 2 mm. or more within the border of the left cardiac silhouette. It was diagnosed in 13 of 2,000 patients. Pericardicentesis was performed in 7 of the 13, confirming the diagnosis in 6. In 4 others, findings indicated pericardial effusion. Postmortem examination of 2 others showed Hodgkin's tumor invading the pericardium in 1 and carcinoma of the pericardium in the other.

J. JORGENSEN, R. KUNDEL, and A. LIEBER: The cinefluorographic approach to the diagnosis of pericardial effusion. *Am. J. Roentgenol.* 87:911-916, 1962.

HEMODILUTION PERFUSION for heart surgery gives results in physiologic responses which equal or surpass those from other total-body perfusion techniques. Blood sodium values adjust to normal rapidly and remain there. Good hydration has a protective effect upon renal function. Perfusion is applicable to surgical correction of all congenital heart disorders and to some kinds of acquired heart disease. Dextrose solution is used to prime the pump oxygenator. Equipment is simple, blood requirements are small, and chest-draining losses are slight.

R. A. DEWALL, R. C. LILLEHEI, and R. D. SELLERS: Hemodilution perfusion for open-heart surgery. *New England J. Med.* 266:1078-1084, 1962.

Kernicterus Due to Erythroblastosis Fetalis in Minnesota

A Plea for Alert Management

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KERNICTERUS due to erythroblastosis fetalis can be completely prevented by appropriate alert management of the newborn.¹ The presence in our clinic of several patients with proved kernicterus stimulated the author to review the frequency of its occurrence. The purpose of this article is to present the experience gained. Kernicterus due to erythroblastosis fetalis continues as a problem in Minnesota. It is hoped that the lessons learned from this review will enable us to avoid further occurrence of this preventable condition.

Only kernicterus due to Rh incompatibility has been included in this survey. Obviously, kernicterus is not specifically related only to Rh incompatibility.² It may also occur in ABO incompatibility, congenital spherocytosis, and non-spherocytotic hemolytic anemias, sepsis, hypoxia, and excess vitamin K or sulfisoxazole. These other conditions are not included in this report.

Clinical reliance on the elevated level of bilirubin as being of prognostic importance is further substantiated by this review experience.

METHODS

Definition of kernicterus. Kernicterus is an anatomic finding—yellow staining of certain nuclei of brain, particularly the basal ganglia. This anatomic term has been appropriated to indicate a clinical syndrome. This condition has typical signs—opisthotonus, muscular rigidity, seizures, hypotonia, choreo-athetosis, mental deficiency, dysarthric speech, and hearing loss.²

Chart review. Charts on which a diagnosis of kernicterus was made since 1951 were reviewed. Some of these patients were referred for exchange transfusion in the neonatal period; some for diagnostic purposes because of brain damage; and some for hearing difficulties. To be included in this review, all had to have evidence of increased bilirubin. Some of the data were

especially collected from the referring hospital or from the referring doctor. Because of this review, some of the laboratory data were also collected recently as needed for completion of data for this series.

Rh incompatibility. All patients who were included in this study represent proved Rh incompatibility. Clinical Rh incompatibility was diagnosed by a positive direct Coombs' test of the infant, Rh blood group differences between mother and child or the presence of Rh antibodies in the mother, or both of the latter. Many patients whose record did not meet this strict criterion were excluded.

RESULTS OF SURVEY

The results of the survey are presented in table 1. The most important observation is that half of the neonatal disasters occurred within the last four years. All these patients have severe brain damage. Some of the symptoms included opisthotonus, seizure, spasticity, and athetosis. Among patients tested, 6 had obvious evidence of hearing loss. All these patients have severe brain damage. Kernicterus was, therefore, clearly apparent to the trained eye.

The highest recorded bilirubin levels are presented. This does not mean that those recorded were the very highest peak of bilirubin, since determinations were not done at all in some and in others, determinations were done late, after transferring the patient to another institution. In 7 of these patients, bilirubin levels were over 20 mg. per cent. These data clearly show the critical level of bilirubin in these infants. For 1 patient, bilirubin determination was done only at age 9 days; 2 patients had no bilirubin test. History was indicative of the presence of jaundice. These data provide further substantiation that the common denominator among these patients is the elevated serum bilirubin.³

Very few direct Coombs' tests were done on the first days of life.

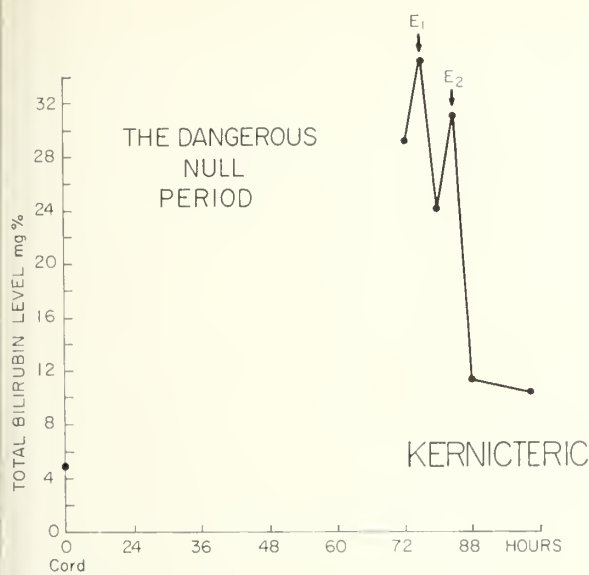
In some instances, maternal titer determina-

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TABLE 1

Year of birth	Evidence of kernicterus	Birth weight in gmi.	Highest total bilirubin, mg. per cent	Clinical jaundice	Patient blood type	Direct Coombs	Mother's blood type	Mother's titer
1961	Absent Moro, irritable, 2 days of age. Autopsy: typical brain nuclear staining of kernicterus	3,600	29.4		Gr: O, CDE/cde	+	Gr: O, cde/cde	1:156
1960	Seizure 4 months of age; 10 months of age muscle weakness	2,180	30.5		Gr: B, CDE/cde	+	Gr: O, cde/cde	Antibody present
1960	Opisthotonus present 2½ months of age. Hearing difficulty at 15 months of age	3,391	35.2		Gr: B, CDE/cde	+	Gr: B, cde/cde	Antibody present
1957	At present, in institution because severe retardation, spasticity, hearing loss	2,041	27.4		Gr: O, Rh+	+	Gr: A, Rh—	
1957	Opisthotonus, icteric spastic quadriplegia present at 2 months of age	4,082	30.4		Gr: O, cDE/cde	+	Gr: A, cde/cde	1:32
1956	Opisthotonus present at 3 weeks of age. Full term Extensor spasms, severe hearing loss, athetosis at 3 years of age		64.0		Gr: O, A, MsMs, CDE/cde K—, Fy (a+) Jk (a—b+)	+	Gr: O, A, MsMs CDE/cde K—, Fy (a+) Jk (a—b+)	1:16 (Anti JKa+)
1955	Bilateral hearing loss and no speech at 3 years of age	1,785	22.0		Gr: O, CDE/cde		Gr: O, cde/cde	1:32
1953	Cannot hold her head, spasticity, mental retardation at 2 years of age	3,061	15.2*	From second day, orange yellow	Gr: O, Rh+	+	Gr: O, Rh—	1:32
1951	Mild spasticity at 9 years of age. Hearing loss, speech impairment	2,381		Deeply jaundiced	Gr: O, cDE/cde	+	Gr: O, cde/cde	1:1000
1951	Athetosis, poor finger control, decreased hearing, speech impairment at 8 years of age	3,430		Severe jaundice from secondary until 10 days	Gr: O, CDE/cde	+	Gr: O, cde/cde	1:4

*Level of bilirubin taken until 9 days of age



Bilirubin values for infant presented in case report

tions were not done until a considerable length of time after birth.

Four of the infants reviewed in this study were premature.

REPORT OF A CASE

Twelve hours after birth, this infant (table 1, case 3) was noted to be definitely jaundiced. Past history indicated that 1 previous infant had needed exchange transfusion. The mother was Rh negative and had increased antibody titer and the father was Rh positive. The cord bilirubin at birth was 4.7 mg. per cent and the direct Coombs' test was positive. On the third day of life, the baby had an obvious pumpkin-yellow color. No bilirubin values were obtained during this "null" period (see figure). Exchange was attempted but was not successful and the baby was transferred. The baby's blood type was group B, CDe/cde. Hemoglobin was 7.6 gm. per cent. Immediately before exchange transfusion, the bilirubin was 35.2 mg. per cent. An exchange of 500 cc. of B negative blood was done in two hours. Post-exchange bilirubin levels 24.0 mg. per cent. Another exchange was done of 500 cc. of B negative blood; post-exchange bilirubin was then 11.7 mg. per cent. The bilirubin slowly decreased and within one week was at normal values. During this time, it was observed that the baby was lethargic and that his crying was high pitched and whiny.

Most recently, he was seen at age 15 months; length was 29½ in., weight 19 lb. 7 oz. At that time he could not sit alone. He had begun to grasp objects but could not use any words. At 15 months of age his highest performance was that he recognized parents and followed them with his eyes; otherwise there was no response to the surroundings. Hearing tests revealed profound bilateral loss of acuity. He shows very definite evidence of kernicterus clinically.

DISCUSSION

In 1948, Diamond clearly proved that exchange transfusions can prevent kernicterus. Diamond

and Hsia have shown that the risk of erythroblastosis fetalis increases as the bilirubin level of 20 mg. per cent is exceeded.⁴ Mollison and Cutbush⁵ confirmed this relation between the maximum bilirubin concentration in the plasma and kernicterus (table 2). The indirect bilirubin (unconjugated), found free in the body fluid, is soluble in the brain lipid, and brain damage is the result of the elevation of bilirubin.

Kernicterus can be prevented if the bilirubin level is kept below 20 mg. per cent by exchange transfusion.¹ Repeated transfusion may be necessary. In table 1, 10 severely damaged cases of kernicterus are presented. All had significant damage due to kernicterus. These 10 patients are only a fraction of the many more who were referred to University of Minnesota Hospitals with the same disorder; but, because of inadequate data after birth, the others were excluded.

The case presented here represents a very significant problem of failure to adequately understand the significance of the bilirubin level. The patient was known to have an Rh incompatibility problem because of the previous history of an involved infant. The baby had clear evidence of erythroblastosis fetalis; the direct Coombs' test was positive. The cord bilirubin was 4.7 mg. per cent, which is twice the normal level (normal range 0.7 to 2.8 mg. per cent). Though the patient already had indications at birth for exchange transfusion, this was not done. Despite the above-mentioned data, no sequential bilirubin values were determined. Clinical judgment of the bilirubin level on the basis of appearance of the infant is deceptive and often leads to fatal error. A period of three days left the situation uncontrolled. The child became markedly jaundiced; the bilirubin level went up as high as 35.2 mg. per cent. Despite the therapeutic transfusion endeavors, the level of bilirubin was so high that tragic damage already existed before the exchange transfusion. Kernicterus was not reversible at the late stage.

The present cases show that in some instances, the referring physician knew the problem but

TABLE 2
RELATIONSHIP BETWEEN MAXIMUM BILIRUBIN
CONCENTRATION IN THE PLASMA
AND KERNICTERUS²

Maximum bilirubin concentration mg. per 100 cc.	Total number of cases	Number with kernicterus	Per cent with kernicterus
30 to 40	11	8	70
25 to 29	12	4	33
19 to 24	13	1	8
10 to 18	24	0	0

either he did not seize the appropriate initiative or he did not order the necessary laboratory and hematology studies. Further, the physician did not do exchange transfusion or, if he did, the bilirubin level was too high to avoid damage. In other cases the problem was not even considered as a possibility. In order to prevent and to be ready for the necessary action, the following recommendations are made:

Blood type and Rh factors should be done initially for every pregnant woman. If she is Rh negative, the father's blood should be grouped and typed. If he is Rh positive, the pregnant woman's blood should be tested for presence of Rh antibodies. Another specimen should be sent to the laboratory at the thirty-fourth, thirty-eighth and fortieth week of pregnancy for antibody titration.* This is done because evidence of sensitivity may not occur until late pregnancy.

In cases where Rh incompatibility is possible, the exchange might be necessary soon after birth. The infant has to be judged individually and the physician must be fully prepared for full therapeutic care for exchange transfusion. The decision depends on the outcome of the previous pregnancy and the condition of the present newborn. Cord bilirubin, hemoglobin, and Coombs' test should be done. If, on the basis of these data, the exchange transfusion does not seem indicated, sequential bilirubin levels are indicated in order to observe any sudden rise in the bilirubin level. Clinical observation alone regarding severity of the jaundice is misleading. Close follow-up of bilirubin values is absolutely necessary to predict an increase and to prevent the level from going over 20 mg. per cent.

Indications for exchange transfusion. Hydrops fetalis is, of course, a major indication for exchange transfusion. Also, in cases where the Coombs' test is positive and cord bilirubin is over 4 mg. per cent or cord hemoglobin is under 12 gm. per cent, exchange transfusion is indicated. More consideration should be given premature infants. In addition, if the increase in bilirubin shows that the level is going to rise above 20 mg. per cent, exchange should be strongly considered.

In normal circumstances, the peak of the bili-

*Necessary tests can be performed at War Memorial Blood Bank, 2304 Park Avenue, Minneapolis 4, Minn. Clotted blood from the mother (8 to 10 cc.) may be mailed to them for routine blood grouping, Rh determination, and screening for Rh and other blood group antibodies. Later on, if necessary, additional specimens taken during pregnancy, at the time of delivery, and post partum can be tested. A container is furnished and results are mailed or, in emergencies, telephoned. A \$5 charge will include all above-mentioned tests per pregnancy.

rubin for a full-term infant should be at the third day and the premature at the fifth day after birth. The hemoglobin is unreliable because it does not reflect existing hemolysis and stable hemoglobin does not exclude increased bilirubin levels.

The disastrous personal effect of the kernicterus for the patient, for his family, for his doctor, and for the community cannot be overemphasized.

SUMMARY

Kernicterus represents an obvious syndrome manifested by mental retardation, spasticity, hearing loss, or athetosis. Kernicterus due to elevated bilirubin can be prevented by adequate and repeated exchange transfusions. The disorder, however, still remains a clinical problem.

A significant number of patients referred to the University Hospitals have residual damage from kernicterus. This indicates that the implications of bilirubin level have not been fully appreciated. Table 1 briefly outlines experience with some recent patients. One patient is presented in more detail; because of failure to prevent elevated bilirubin level with exchange transfusion, the patient is totally debilitated.

Reasons for inadequate management include failure to identify mother's Rh type and titer, inadequate observations of level of bilirubin of the newborn infant, and no action or delayed action in institution of exchange transfusion. Rh types and antibody titer can be easily obtained in Minnesota at minimal expense. A resource for such tests is included in this article for those physicians who do not have local facilities.

A plea is made for more interested observations and action in the newborn period so as to prevent future occurrence of the disorders presented here.

We wish to acknowledge the following granting agencies for their support in making these studies possible: United States Public Health Service (H-3107) (H-5341) (AM-02917-04) and Minnesota Division, American Cancer Society.

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Epsilon-Aminocaproic Acid for Hematuria in Hemophilia

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EPSILON-AMINOCAPROIC ACID (EACA) decreases bleeding when a pathologic amount of plasminogen activator activity is present.^{1,2} EACA exerts this beneficial effect on abnormal fibrinolysis by inhibiting plasminogen activator activity.³ The therapeutic administration of EACA returns the unbalanced fibrinolytic mechanism to a physiologic status. Fibrin deposits remain intact and bleeding ceases.⁴

The urinary tract is an unusual site of bleeding because normally it has a high content of plasminogen activator.⁵ This urinary plasminogen activator (urokinase) is easily detected in fresh normal urine. Urokinase thus places the genitourinary tract at a hemostatic disadvantage. This fibrinolytic imbalance has been shown to be corrected by EACA in postprostatectomy patients.^{6,7}

Genitourinary tract bleeding in hemophilias has generally not responded to plasma therapy.⁸ The continued genitourinary bleeding in the hemophiliac could be caused by the imbalance produced by the urokinase present. Since EACA inhibits urokinase activity, EACA might effectively reduce hematuria in hemophilias.

CASE REPORTS

This is a report of EACA therapy in 3 males with antihemophilic globulin-deficient classical hemophilia who had persistent hematuria. Each had cessation of hematuria after infusion of EACA. Plasma was not given immediately before or concurrently with the EACA infusions.

Case 1. I. H., a 21-year-old male with antihemophilic globulin-deficient hemophilia, had had hematuria for one week's duration. His past history and family history were classical for antihemophilic globulin hemophilia.

Thromboplastin generation test (TGT) was recorded as 32.5 seconds per six minutes (control, 13.2 seconds per four minutes). His abnormal TGT was corrected by normal adsorbed plasma and not by serum. Lee-White clotting time was 70 minutes.

On January 21, 1962, the patient had spontaneous gross hematuria of three days' duration, accompanied by right flank discomfort. On an outpatient basis, he was given 2 units of fresh-frozen plasma. He remained in bed at home. His urine cleared temporarily. On January 27, gross hematuria again occurred and he received another 2 units of fresh-frozen plasma. Finally, he was admitted to the hospital on January 28 because of persistence of urinary tract bleeding.

Physical examination revealed a bruise over the left and right shoulders, moderate right costovertebral angle tenderness, and a grade II/VI systolic murmur at the base of the heart. Hemoglobin was 13.5 gm. per cent; blood urea nitrogen was 14 mg. per cent; and creatinine was 1.5 mg. per cent. Urine culture was sterile. Films of the abdomen revealed no radiopaque stones.

Two units of fresh-frozen plasma were given on each of his first four hospital days. Hematuria persisted until the fifth day, when only microscopic hematuria was present.

However, on the sixth hospital day, gross hematuria recurred. The patient was given 4 units of plasma during the seventh and eighth days without effect on hematuria.

After the eighth day, no fresh plasma was used in treatment. Urine was collected in twelve-hour periods, and total hemoglobin in urine was measured for each twelve-hour specimen. On the eleventh hospital day (over forty-eight hours after last plasma therapy), he was given EACA intravenously in 5 per cent dextrose in water. A total of 8 gm. in 1,200 cc. over a twelve-hour period was given.

Gross hematuria cleared markedly during the

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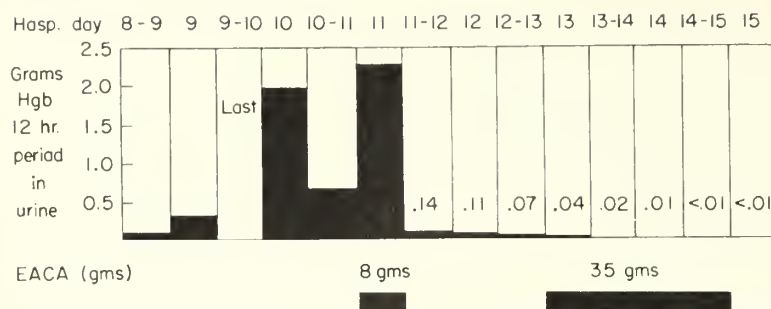


Fig. 1. Graphic demonstration of reduction of hemoglobin loss in urine in patient 1 with hemophilia after treatment with EACA (epsilon amino-caproic acid)

last few hours of the infusion. On the thirteenth hospital day, EACA as an intravenous drip was again started. The patient then received a total of 35 gm. over the next forty-eight hours. The reduction of the hematuria in relation to the EACA therapy is summarized graphically in figure 1.

After the second course of EACA, frequent examinations of the urine sediment revealed no red blood cells. Subsequent studies included a normal intravenous pyelogram.

Circulating antieoagulant (anti-antihemophilic globulin factor) was not present. Dilutions of the patient's plasma did not produce an abnormal partial thromboplastin time in normal plasma. Correction of the patient's partial thromboplastin test was obtained after administration of a unit of fresh-frozen plasma.

Case 2. L. F., a 21-year-old male, was antihemophilic globulin deficient and had severe lumbar pain and hematuria.

Two days before the present admission, right lumbar pain developed after sitting down forcefully. The next day, radiating pain accompanied by dysuria and gross hematuria was noted. Physical examination at the time of admission on February 23 revealed tenderness over the right lumbar region and mild flexion deformities of the knees. Urine was grossly bloody. An in-

travenous pyelogram showed incomplete obstruction of the right ureter by a retroperitoneal hematoma. He received 2 units of fresh-frozen plasma on the first hospital day and 3 units on the second day. The hematuria persisted. He was given 2 units of fresh whole blood which produced transient clearing of hematuria. Gross hematuria recurred on the sixth hospital day.

Urine hemoglobins were measured on the eighth and ninth days while the patient remained in bed; no more plasma or blood was given. On his tenth hospital day, an infusion of 15 gm. of EACA in a 5 per cent solution was given over a twenty-four hour period. Urine was grossly bloody during the first six to eight hours of the infusion but gradually cleared. At the end of the infusion, the urine was grossly clear and the sediment had 2 plus red cells on microscopic examination. The following day, there was 1 plus red blood cells in the sediment. He received another 7.5 gm. of EACA over a twelve-hour period, and subsequent urine sediments showed no red blood cells. This is summarized graphically in figure 2.

Case 3. M. F., an 8-year-old male, had a history of easy bruising since birth. Laboratory evaluation of his coagulation deficit revealed classic antihemophilic globulin-deficient hemophilia. Three days before his recent admission,

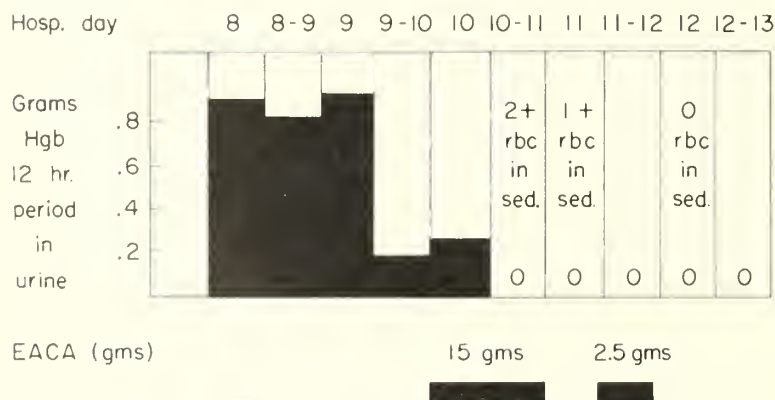
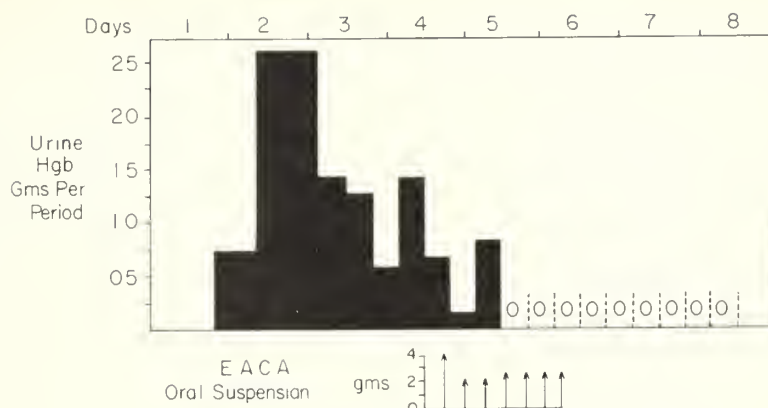


Fig. 2. Patient 2 is a 21-year-old male who was AHG hemophilic and who responded to EACA therapy over a twenty-four-hour urine period. His urine was grossly bloody during the first six hours of EACA infusion, but at the end of twenty-four hours the urine was grossly clear.

Fig. 3. Outline of results of therapy in an 8-year-old male who received only EACA during this time and only after a suitable control period had been established. Again, there is a marked improvement in the reduction of the urinary bleeding following institution of EACA therapy.



he noted intermittent right lumbar pain. There had been no history of trauma. The day before admission, hematuria was noted. No other symptoms of urinary tract dysfunction were elicited. The physical examination revealed a few bruises and a deformed left knee, the residua of a previous hemarthrosis. His hemoglobin was 10.5 gm. per cent at the time of admission and varied only slightly during his hospital stay. Urinalysis revealed a grossly bloody urine with 3 plus red blood cells on microscopic examination of the sediment.

He was allowed full activity throughout control periods and periods of therapy. No transfusions of blood or plasma were given. The only medication he received was EACA which was begun after a suitable control period had been established. The data are summarized in figure 3.

Sixteen hours after initiation of treatment with an oral suspension of EACA, the hematuria ceased and no blood was noted in the urine during the subsequent seventy-two-hour period of observation.

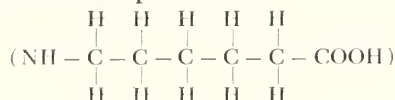
Urokinase. Urokinase was measured by direct pipetting of fresh urine on Astrup fibrin plates. EACA was effective in reducing the area of lysis from 841 mm.² to 312 mm.² at the height of infusion in patient 2. A similar inhibition of lysis of fibrin plates was found in urine of patient 1 after EACA infusion.

DISCUSSION

Three classical hemophilia patients had cessation of hematuria when treated with epsilon-aminocaproic acid. The beneficial results were not due to plasma therapy, since the first 2 had received none for two days and the third had no plasma before administration of EACA. The hypothesis is that EACA inhibited the urokinase

normally formed in the urine and this prevented lysis of fibrin.

Epsilon-aminocaproic acid



is a monoamino carboxylic acid that inhibits plasminogen activator activity in a competitive manner.³ Others have indicated the possibility that inhibition of plasmin is also possible at the same concentrations of EACA which are required for inhibition of plasminogen activators.⁹

Because of the failure of hemostasis in the urinary tract due to urokinase, McNicol and associates⁶ administered EACA after prostatic surgery. The EACA significantly reduced postoperative bleeding. Sack and co-workers⁷ confirmed this finding. The theoretic mechanism whereby EACA improved postprostatectomy hemostasis is not completely identified at present.¹⁰

This report indicates a possible use for EACA in hemophilic hematuria. The rationale is to inhibit the normal amounts of urokinase and thus preserve the fibrin formed over the bleeding sites.^{11,12}

Preliminary considerations for use of this type of therapy for hemostasis in similar circumstances have been presented elsewhere.^{13,15,16} More observations are needed and this communication is intended to encourage further clinical investigative use of EACA by others.

Further data will also be needed to determine if the marked elevations of the tissue levels of EACA¹¹ are responsible for the salutary effect noted.

This study was supported by United States Public Health Service grants No. A-2917 (C2) and H-5341 (C2) and by the Minnesota Division, American Cancer Society.

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PANCREATIC DUCT decompression relieves chronic relapsing pancreatitis. Drainage is made through the papilla of Vater when the disease is in an early stage. Retrograde drainage should be reserved for clear-cut obstruction within the gland. Diversion of an incompletely obstructed duct may increase susceptibility to duodenal ulcer. In caudal pancreatectomy and retrograde pancreaticojejunostomy, the spleen and islet-bearing tissue in the tail of the pancreas must be removed if there is diabetes. They are not removed when the pancreas is approached from the anterior surface. Side-to-side pancreaticojejunostomies were done during a four-year period in 6 patients with advanced chronic pancreatitis. None has had recurrence of pain.

A. P. THAL: A technique for drainage of the obstructed pancreatic duct. *Surgery* 51:313-316, 1962.

HISTOLOGIC EXAMINATION is the only reliable method for distinguishing benign proliferative fasciitis from a malignant neoplasm. It eliminates unnecessary radical excision, irradiation, and chemotherapy. Simple excisional biopsy is recommended. In a study of 56 patients with lesions in the subcutaneous tissues, involvement of the deep fascia was known in 38, lacking in 2, and not known in 16. Initial diagnosis was correct in only 10 patients; in 38 the lesions had been considered malignant. Twelve who had radical local excision with or without skin graft have had no recurrence for one to twenty-eight years. Four who had radiation therapy after local excision have had no recurrence for six to nineteen years.

E. H. SOULE: Proliferative (nodular) fasciitis. *Arch. Path.* 73:437-444, 1962.

The Antiglobulin or Coombs' Consumption Test and the Diagnosis of ABO Hemolytic Disease of the Newborn

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COOMBS' consumption technic, a method for detecting sensitization of erythrocytes by antibody, was first described by F. Stratton.¹ "Coated" or "sensitized" erythrocytes produce varying degrees of neutralization of a known amount of antiglobulin antibodies. The measurement of the residual antiglobulin after partial neutralization provides a means for detection of the presence of coating of the cells by globulin (antibody). This is the basic principle of the "Coombs' or antiglobulin consumption test" developed by Moulinier² and Steffen³ to detect platelet antibodies and leukocyte antibodies.^{4,5} The purpose of this paper is to explain the Coombs' consumption test and to present preliminary results of its application in the diagnosis of ABO hemolytic disease of the newborn.

In vitro demonstration of coating of cells by antibody. Nonagglutinating antibodies can produce in vitro or in vivo or both types of "coating" of cells containing the corresponding antigen. There are 3 "in vitro" methods for the demonstration of coating of cells by nonagglutinating antibody.

1. Direct antiglobulin reaction (Coombs' reaction): In this reaction the cells containing the antigen are coated by antibody. When mixed with antihuman globulin, agglutination is produced (figure 1).

2. Elution method: By means of a physical method, for example, heat,⁶ the antigen-antibody reaction is dissociated and the cells (antigen) can be separated from the supernatant-eluate (antibody) by centrifugation. Tests of eluate are performed with cells of known antigenic make-up followed by antiglobulin reaction (figure 2).

3. Antiglobulin or Coombs' consumption test: In this test, the same reagent of the antiglobulin

reaction is used but the amount of antihuman globulin antibody neutralized by the cells coated with antibody is measured indirectly. Therefore, if the cells are coated by antibody they will react with some of the antihuman globulin (Coombs' consumption). The Coombs' consumption test consists of measuring the amount of antihuman globulin left after partial neutralization by the coated cells. Essentially, the cells in question are mixed with a known amount of antihuman globulin (for example, 100 units). After incubation, the measurement of the amount of antihuman globulin left (50 units) indicates the amount taken up or consumed by the cells (figure 3).

The amount of antihuman globulin present before and after treatment with coated and uncoated cells can be measured by (1) titration in twofold dilutions using erythrocytes known to be coated by nonagglutinating antibodies. The highest dilution of the antiglobulin serum which still agglutinates the red cells indicates the serum's content of antiglobulin; and (2) the avidity method,⁷ which consists of assaying the interval between the mixing of antihuman globulin with the detector cells (antibody-coated erythrocytes) and the beginning of the agglutination of the cells. There is a direct relationship between the inverse of this time and the concentration of antiglobulin.

Application of the Coombs' consumption test. The following outline briefly presents the major applications of the Coombs' consumption test:

A. Demonstration of platelet and leukocyte antibodies.¹⁻⁴ Both the test platelets and the test leukocytes tend to agglutinate spontaneously. This self-agglutinating phenomenon is difficult to control. For this reason, the method of choice for demonstration of platelets and leukocyte antibodies is the Coombs' consumption test.

B. Measurement of degree of sensitization of erythrocytes by nonagglutinating antibody.^{1,6}

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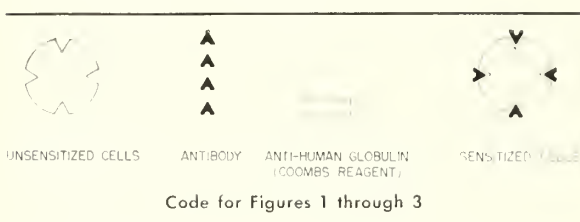
C. Identification of protein component coating the erythrocytes of auto-immune hemolytic anemia.⁸ In this disease the patient's erythrocytes may be coated by globulins of small molecular size (7S gamma globulin) or by larger molecules (19S or 21S) having different specificity.

D. Demonstration of common antigens of erythrocytes in platelets, leukocytes, or other cells.⁸ The platelets or leukocytes are treated with an antisera containing a known antibody against a red cell antigen, such as anti-A. During a second step, these cells are tested for "coating." If they produce positive consumption they contain a common antigen with the red cells.

E. In the diagnosis of ABO hemolytic disease of the newborn. The demonstration of antibodies coating the erythrocytes of newborn infants with ABO hemolytic disease is always difficult. The direct antiglobulin or Coombs' test is usually negative.^{9,10} A negative direct Coombs' test does not rule out the disease. In some cases of ABO hemolytic disease of the newborn with negative Coombs' test, coating of the erythrocytes can be demonstrated by elution of the erythrocytes and by the Coombs' consumption test.⁸

MATERIAL AND METHODS

Preparation of detector cells. The materials used included: antihuman globulin reagents



with titers of 1:128 to 1:196; nonagglutinating (incomplete) anti-Rh antibody with a Coombs' titer of more than 1:2,000; group O, Rh positive (R₁R₁) human erythrocytes collected in one-tenth volume of a 2 per cent solution of ethylenediaminetetraacetic acid (EDTA). For sensitization, 0.1 ml. of the nonagglutinating anti-Rh serum was added to 1 ml. of a 50 per cent concentration of washed red blood cells and mixed thoroughly. The mixture was incubated for one hour at 37° C., then washed five times with normal saline, and finally made into a 4 per cent suspension in normal saline.

Clinical material. Three ml. of cord blood from each of 6 patients diagnosed as having

ABO hemolytic disease of the newborn was collected in tubes containing EDTA anticoagulant. Control cord blood was similarly collected from unaffected infants. The cells were washed five times in normal saline.

Method. The method used involves packing 0.6 ml. of washed erythrocytes from the patient in a Wintrobe hematocrit tube and 0.6 ml. of washed erythrocytes from the control in a second hematocrit tube. Next, 0.4 ml. of antihuman globulin is added to each tube and mixed thoroughly with a capillary pipet. The mixture is incubated at room temperature for thirty minutes and then centrifuged for ten minutes. This is followed by measurement of the antiglobulin content of the supernatant fluid. The antiglobulin content is assayed by titration of



Fig. 1. Direct Coombs' test: the red cells that are coated with the antibody are agglutinated directly by application of the Coombs' sera.



Fig. 2. Elution test: by means of heat the antibody is removed by elution and this can then be measured.

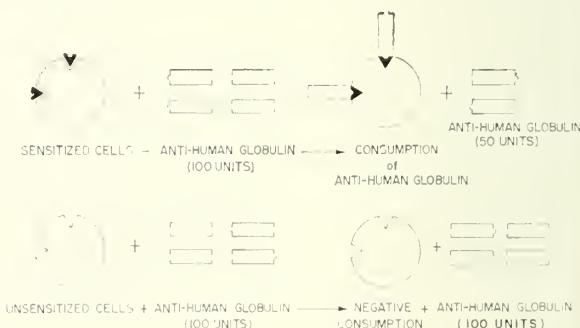


Fig. 3. The Coombs' consumption technique: the amount of Coombs' antibody that has or has not been used in agglutinating the sensitized cells is measured. In the example given above, the first set illustrates the fact that because a sensitizing antibody was present on the patient's red cells, the Coombs' antiglobulin sera was utilized. The Coombs' sera was reduced from 100 to 50 units. In the bottom example, the Coombs' sera was not utilized and therefore there was still as much of the sera at the end as at the beginning of the test (100 units). The latter is a negative test.

SIX CASES OF ABO HEMOLYTIC DISEASE OF NEWBORN
WITH NEGATIVE COOMBS' TEST AND POSITIVE
COOMBS' CONSUMPTION TEST

	Mother's group	Baby's group	Direct antiglobulin test	Coombs' consump- tion test
Case 1	O	A	Negative	+
Case 2	O	B	Negative	+
Case 3	O	A	Negative	+
Case 4	O	A	Negative	+
Case 5	O	B	Negative	+
Case 6	O	A	Negative	+

twofold dilutions and each dilution is tested with the "detector cells."

The Coombs' consumption value was obtained by using the formula $\frac{C-P}{C} \times 100$, with C being amount of antiglobulin measured after treatment with control cells, and P, amount of antiglobulin measured after treatment with patient's cells.

RESULTS

The 6 patients included in this study illustrate selected cases of ABO hemolytic disease of the newborn seen at the University of Minnesota hospitals. All 6 patients showed a negative direct Coombs' test. The criteria for diagnosis of the disease was the presence of (1) ABO incompatibility between infant and mother; (2) a positive partial neutralization test with Witebsky substance in the mother's serum; (3) jaundice in the baby; (4) incompatible iso-agglutinin free in the cord serum of the affected infants; and (5) a positive specific activity in the eluate from the cord erythrocytes. Despite the fact that all these children showed a negative direct Coombs' test, the results of the Coombs' consumption test were positive (see table).

DISCUSSION AND SUMMARY

Experimentally, one can demonstrate⁸ that it is possible to find a negative direct Coombs' test

and a positive Coombs' consumption test of the erythrocytes in question. Either there are few cells coated with antibody at birth or the coating of the erythrocytes of the infant by incompatible iso-agglutinin is in small amounts. The antiglobulin consumption test is more sensitive than the direct antiglobulin reaction because it can detect smaller amounts of globulin coating the cells. It uses a large proportion of cells in comparison with the amount of antihuman globulin.

A review of the Coombs' consumption test is presented with its applications. The preliminary results of the application of Coombs' consumption test in ABO hemolytic disease are reported.

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Methemoglobinemia and Hemolytic Anemia in Normal Newborns and Normal Prematures

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THE occurrence of methemoglobinemia in several babies in a newborn nursery in a local hospital is the subject of this report. The methemoglobinemia with resulting hemolytic anemia and jaundice in these infants presents thus another, though probably infrequent, cause of hemolytic disease of the newborn which must be considered when other more likely causes are not present.

Though exposure to hemolytic drugs and toxic substances is a relatively common cause of hemolytic anemia, it is rarely considered to be a factor in anemia in the newborn.¹ Although no single toxic substance could be specifically incriminated in the nursery of the hospital where these babies were observed, it is considered that the methemoglobinemia and hemolytic phenomenon were the result of either an accumulation of toxic products or the accumulation of a similar toxin in several products. Whether these toxic substances were orally ingested by the babies or absorbed through their skin has not been established. This report is limited to the discussion of the hemolytic anemia and methemoglobinemia which occurred. The results of the investigation of the multiple products to which the babies were exposed in the nursery will be published in a subsequent report.

All the infants with methemoglobinemia were observed during a five-week period from September 1961 through October 21, 1961. After this latter date, there were no more infants with methemoglobinemia, probably as a result of changes and simplification of laundry procedures.

A total of 16 infants in the newborn nursery

were found to exhibit methemoglobinemia and hemolytic anemia. Ten of the infants were premature by weight (below 2,500 gm.); the 6 premature infants selected for discussion in this report were those with sufficient recorded laboratory data.

METHODS

Methemoglobin determinations were done both spectrophotometrically and also by the method of Evelyn and Malloy.² A Beckman DK2 recording spectrophotometer was used for determining absorption of ultraviolet light over the wave length of 500 to 700 m μ . Methemoglobin which is absorbed at 630 m μ , was differentiated from other abnormal hemoglobin pigments by its prompt conversion to cyanmethemoglobin after addition of potassium cyanide. This method was used as a qualitative method for the detection of methemoglobin, and the Evelyn and Malloy method was utilized for quantitative determinations. Hemoglobin levels were determined by the cyanmethemoglobin method.³ Reticulocytes were determined by staining blood smears with brilliant cresyl blue. Serum bilirubin was determined by the Evelyn and Malloy method.^{4,5}

PATIENTS

A summary of the pertinent laboratory data from the infants is presented in table 1. All of the infants included were premature by weight and in all, the most obvious presenting sign was a grayish-blue cyanosis. In addition, all but one infant were visibly jaundiced. There were no evidences of cardiac or respiratory diseases. The general physical activity of the infants was thought to be normal for the age and weight.

A remarkably consistent pattern was present in all of the babies. Evidence of methemoglobinemia was observed late in the first week of life and, almost simultaneously, clinical jaundice

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and elevated serum bilirubin levels were observed. There was a prompt reduction in methemoglobin levels after therapy with methylene blue, but whether this therapy was given or not, significant anemia developed. The hemoglobins reached their severe low levels (see table) at approximately 1 month of age. The evidences of hemolytic anemia included hyperbilirubinemia, anemia, and reticulocytosis. The striking reticulocytosis of girl B (table) on the fourteenth day of life when 80 per cent of the peripheral red blood cells were reticulocytes is a convincing demonstration of the ability of this premature infant to respond promptly to anemia.

CASE REPORT

The clinical course of 1 illustrative case is presented in some detail.

Girl B (case 1) was born prematurely after an otherwise normal gestation. The birth weight was 3 lb. 14 oz., and the immediate neonatal period was normal. She was kept in an isolette and on the third day of feedings with modified cow's milk (Similac) by gavage were initiated. There were no unusual symptoms until the seventh day of life, when cyanosis was noted. The infant was treated with multiple antibiotics; however, there was no change in the baby's color. Roentgenograms of the chest were considered within normal limits. When the baby was 12 days of age, a hemoglobin level of 12 gm. per cent was found, as compared with a level of 17.2 gm. at birth. The diagnosis of methemoglobinemia was considered at this time and it was found that 13 per cent of the total hemoglobin was methemoglobin. The baby was treated with 1 per cent methylene blue, 2 ml. per kilogram intravenously, which resulted in a prompt return of the infant's color to normal. A total of 50 ml. of vitamin C and 5 drops of

1 per cent methylene blue were given daily. At 17 days of age, or 5 days after beginning therapy, the hemoglobin was found to be 4.3 gm. per cent. Reticulocyte count at this time was 80 per cent (table) and many of the red cells exhibited Heinz bodies. All medication was discontinued at this time. The baby was placed on an oral iron preparation and discharged from the nursery at 1 month of age. When observed at 6 months of age, the infant had developed normally and her hemoglobin was 9.7 gm.

DISCUSSION

After the initial intravenous therapy, 4 of the babies included in this report were continued on oral methylene blue. There is a possibility that the methylene blue itself, while not the initiating cause of the severe hemolytic anemia, may have increased the severity of the anemia.⁶ The development of severe anemia in the 2 infants who did not receive methylene blue therapy would indicate that hemolysis due to methylene blue was not a serious factor. While newborns, and in particular premature infants, normally have levels of methemoglobin higher than adults, the levels exhibited by these infants were well above the normal range.^{7,8} One reason that the most severe anemia was observed in the premature population of the nursery was probably the decreased ability of the prematures' red cells to reduce methemoglobin to ferrous hemoglobin reflecting an immaturity of the necessary enzyme systems including methemoglobin reductase activity.^{9,10} The toxic effects would be manifested in prematures and not other patients exposed to a similar quantity of atoxic material as a result of this enzyme immaturity. The premature infant, therefore, may function in the hospital as the first indicator of toxin accumulation.

TABLE
LABORATORY DATA FOR 6 INFANTS WITH METHEMOGLOBINEMIA

Case	Birth weight	Hemoglobin		Reticulocytes, % (normal = under 10%)	Bilirubin		Methemoglobin		Treatment
		Value, gm. %	Age, days		Highest value, mg.	Age, days	Per cent (normal = under 1%)	Age, days	
1	3 lb. 4 oz.	17.2 4.3	1 16	80	1.7/17.1	10	13	12	Methylene blue Vitamin C
2	4 lb. 4 oz.	20.4 4.8	1 20	30	5.2/24.0	26	15.3	10	Methylene blue Vitamin C
3	3 lb. 9 oz.	17.7 5.5	1 21	16.2	0.8/24.8	16	12	7	Methylene blue Vitamin C
4	4 lb. 1 oz.	12.9 6.2	1 21	19	0.5/16.0	13	19	7	Vitamin C
5	3 lb. 8 oz.	18.4 7.4	1 30	7.3	1.4/30.2	12	30	4	Methylene blue
6	3 lb. 4½ oz.	17.9 7.9	1 48	9.3	0.9/ 1.25	48	6	—	Vitamin C

SUMMARY

The laboratory results, clinical findings, therapy, and course of 6 premature infants with methemoglobinemia and hemolytic anemia were described.

Although no specific toxic substance has been positively identified, the observed phenomenon abruptly ceased after there was radical alteration in procedures in the hospital laundry and nursery. A possible explanation for the outbreak seems to be that there had been an accumulation of toxic exposures in the infants.

There was striking evidence of hemopoietic response to anemia in these premature infants.

This outbreak serves to point out the possibility of methemoglobinemia in cases of unexplained hemolytic anemia in newborns, especially if there is associated cyanosis.

ADDENDUM

T.C.C. (Tri-chlorocarbonanilide) was used in the laundry processing of the nursery linen. T.C.C. was discontinued when the present epidemic of methemoglobin and anemia occurred.

While this manuscript was in press, Dr. Benjamin A. Kagan reported that the T.C.C. can cause degradation of this chemical to chloraniline, which, in turn through skin absorption, may produce sufficient methemoglobin anemia to result in clinical cyanosis and anemia. Thus far there have been about 18 cases detected from 3 hospitals throughout the United States. This was

the publicized statement on cyanosis in premature and newborn infants from the subcommittee of accidental poisoning, dated June 26, 1962.

The epidemiologic and laboratory experimental work concerning the pathogenesis of this occurrence of methemoglobinemia will be the subject of another article.

The recognition of an epidemic-type problem by Drs. Eldon B. Berglund and Allyn C. Bridge initiated these studies. We gratefully acknowledge the support and assistance provided by Drs. Berglund and Bridge.

Dr. Paul R. Finley, under whose supervision most of the laboratory determinations were done, is to be especially thanked.

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TEMPORARY ANOVULATION for treatment of endometriosis is safely induced by Norethynodrel. Mild nausea and breast engorgement, if occurring, disappear within a week. Twenty-two patients were given 20 mg. for sixty to one hundred twenty consecutive days, a smaller amount than in previous studies. Of the 20 women completing the course, 19 had no pain or palpable disease when examined two to thirty-one months later. One, who had had therapy for only sixty days, reported pain, but endometriosis did not recur. Bleeding in one instance was controlled by increasing dosage to 40 mg. Two patients became pregnant within four to five months after therapy.

B. F. P. WILLIAMS: Conservative treatment of endometriosis with progestin therapy. *Am. J. Obst. & Gynec.* 83:715-719, 1962.

Diagnostic Confusion Associated with Spherocytes in Coombs'-Positive Acquired Hemolytic Anemia

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SPHEROCYTES are frequently present in acquired Coombs'-positive hemolytic anemia. These spherocytes morphologically cannot be differentiated from those seen in familial spherocytic hemolytic anemia.

Eleven patients with a diagnosis of acquired Coombs'-positive hemolytic anemia have been treated in the Department of Pediatrics of the University of Minnesota over the last ten years. Half of these patients were referred with a diagnosis of familial spherocytic hemolytic anemia. This diagnostic confusion arises from the interpretation of the blood smears seen in the two entities. Clearly, spherocytes are not pathognomonic of hereditary spherocytic hemolytic anemia. This diagnostic mistake may be particularly unfortunate since it not only delays proper therapy for the acquired disease but may subject the patient to unnecessary splenectomy. This prospect, coupled with the excellent prognosis of even the severe acquired hemolytic anemia when treated with persistence and rational management, would justify any diagnostic procedure needed to differentiate these diseases. The one test which will differentiate them is the simple Coombs' test.

The peripheral blood smear and bone marrow examination which are so reliable in most hematologic disorders cannot differentiate Coombs'-positive acquired hemolytic anemia from spherocytic familial hemolytic anemia. These examinations will give evidence of increased erythrocyte production, and this, coupled with a low hemoglobin without evidence of bleeding, will only broadly suggest a hemolytic process.

REPORT OF CASE

The following is the case report of a typical patient with acquired hemolytic anemia.

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C. A. was first noted to be anemic at 22 months of age. Hemoglobin at that time was 7.0 gm. per cent, and she was empirically treated with iron. One month after the onset of therapy she was noted to be jaundiced; her hemoglobin then was 6.0 gm. per cent. An "iron concentrate" was begun; however, after four weeks, she was more jaundiced and her hemoglobin continued to decrease. She was hospitalized at this time. She was noted to be pale and icteric with no significant physical findings. Bone marrow and peripheral blood smears revealed an erythroid hyperplasia with numerous spherocytes. Her reticulocyte count was 16.8 per cent with a normal cell fragility and sickle-cell preparation. Her icterus index was 41, sulfobromophthalein retention was normal, and cephalin flocculation was 3 plus. With evidence of a normally functioning liver and because of the numerous spherocytes in her peripheral blood, splenectomy was performed.

She was hospitalized for thirty-six of the next one hundred sixteen days. Many transfusions were required to maintain her hemoglobin level. On her last admission to that hospital, the first Coombs' test was performed and was found to be positive. Steroid therapy was instituted. She received 10 mg. of cortisone twice a day. However, on this low dose she had only a partial remission.

A second operation was performed in an attempt to locate an accessory spleen. No splenic tissue was found. A mesenteric node biopsy revealed lymphoid hyperplasia. Following this procedure, her cortisone dosage was increased to 20 mg. three times daily and she was transferred to the University of Minnesota hospitals.

Cortisone medication was continued and an intensive effort to characterize her illness was undertaken. On physical examination she was noted to be somewhat cushingoid but with the exception of her surgical scars and a palpable liver 3 cm. at the right costal margin, there were

CLINICAL AND LABORATORY FINDINGS FOR 11 PATIENTS WITH ACQUIRED COOMBS'-POSITIVE HEMOLYTIC ANEMIA

Patient	Age at onset	Duration (from onset of symptoms until patient demonstrated normal hemoglobin and reticulocytes off medication)	Hemoglobin, gm. per cent		Reticulo- cytes, per cent	Palpable spleen	Palpable liver	Coombs' test	
			High	Low				Direct	Indirect
C. A.	2 yr.	47 mo.	17.8	5.3	83.3	Splenectomy prior to referral	3 cm. ↓	+	+
A. S. B.	2½ yr.	1½ mo.	14.0	4.2	26.8	None	1 cm. ↓	+	—
S. B.	11 mo.	7 mo. Pt. remains symptomatic	16.2	3.9	45.0	3 cm. ↓	No	+	—
D. B.	8 yr.	56 mo.	15.2	4.9	40.5	Splenectomy prior to referral	2 cm. ↓	+	—
E. F.	13 yr.	52 mo. Pt. remains symptomatic	16.0	4.2	63.6	3 times normal size at surgery	None	+	+
R. J.	3½ yr.	Intermittently for 66 mo.	15.6	3.5	32.6	2.5 cm. ↓	2.5 cm. ↓	+	—
V. K.	13 mo.	36 mo.	15.2	3.1	56.6	3 cm. ↓	½ cm. ↓	+	+
D. P.	4½ yr.	4 mo.	14.0	3.2	19.3	None	1 cm. ↓	+	—
Dv. P.	3½ mo.	12 mo.	12.6	6.6	27.8	4 cm.	4 cm. ↓	+	Not done
J. S.	16 yr.	24 days Patient died	12.8	7.5	29.0	None felt	6 cm. ↓	+	—
B. V.	8½ yr.	36 mo.	15.2	6.7	13.8	4 cm. ↓	3 cm. ↓	—	+

*Nitrogen mustard administered intravenously in dosage of 0.4 mg. per kilogram of body weight in 3 divided daily doses

no deviations from the normal. Laboratory investigations on admission revealed a hemoglobin of 17.8 gm. per cent (resultant of transfusions) with a red cell mean corpuscular volume of $89\mu^3$, mean corpuscular hemoglobin of 31.3 $\gamma\gamma$, and mean corpuscular concentration of 35.2 per cent. The reticulocyte count was 7 per cent. Bone marrow and peripheral blood smears revealed an erythrocytic hyperplasia with polychromasia and many Döhle bodies. There were many spherocytes and the suggested diagnosis from the slides was "hemolytic anemia, post-splenectomy picture. It cannot be differentiated from familial hemolytic anemia." A Coombs' test, both direct and indirect, was positive. A test for cold agglutinins was negative.

Radioactive chromium studies proved conclusively the presence of an extraerythrocytic hemolytic disease. This was accomplished by demonstrating a shortened cell survival of Cr^{51} -labeled normal red cells when injected into the patient.

During the first eight days of hospitalization at the University of Minnesota hospitals, the patient's hemoglobin dropped from 17.8 to 5.6 gm. per cent. During this period, peripheral reticulocytosis soared to 83.3 per cent. Cortisone was

increased to 200 mg. per day and she showed general improvement. Her hemoglobin increased and the reticulocyte count decreased. The remaining thirty-six months of her illness were made up of many rapid falls and slow rises in the hemoglobin value. These frequently were directly related to an attempt to decrease the steroid dose. She received, during the last twelve months of this period, 3 separate courses of nitrogen mustard (0.4 mg. per kilogram of body weight in divided doses) but was maintained on steroids throughout her illness. Forty-six months after the onset of illness, the steroid dose was reduced and the patient was able to maintain her hemoglobin with a slightly elevated reticulocyte count. During the last month of the disease, the indirect Coombs' test became negative and her reticulocytes were consistently below 2 per cent. She has remained asymptomatic with normal laboratory findings for six years.

This case, together with those presented in table 1, illustrates the problems associated with the diagnosis and therapeutic management of acquired Coombs'-positive hemolytic anemia. Table 1 represents the patients treated by the University of Minnesota Department of Pediatrics.

<i>Spherocytes in peripheral smear</i>	<i>Mean red cell diameter</i>	<i>Osmotic fragility (per cent)</i>		<i>Duration of steroid therapy</i>	<i>Splenectomy</i>	<i>Comment</i>
		<i>Onset</i>	<i>Complete</i>			
spherocytes are prominent"	5.8 micra	Pt.—0.68 cont.—.50	.36 .34	40 mo.	Yes	Patient received 3 courses nitrogen mustard°
spherocytes are present"	6.2 micra	Pt.—0.42 cont.—.48	.28 .30	1½ mo.	No	
spheroidocytes"	Not done	Pt.—0.80 cont.—0.52	.32 .32	7 mo. Steroids are being withdrawn presently	No	
eros spheroidocytes"	7.0 micra	Pt.—0.46 cont.—.62	.32 .32	49 mo.	Yes	Received 3 courses nitrogen mustard°
roidal erythrocytes seen"	7.8 micra	Pt.—.66 cont.—.52	.32 .32	48 mo.	Yes	Received 3 courses nitrogen mustard° Is now receiving 6-MP and steroids
mentioned	8.2 micra	Pt.—.50 cont.—.50	.30 .28	33 mo.	Yes	Patient demonstrated a leukopenia and thrombocytopenia early in his course
sional spherocytes"	7.6 micra	Pt.—.48 cont.—.52	.32 .30	25 mo.	No	Received 2 courses nitrogen mustard°
sional spherocyte"	Not done	Not done	Not done	1 mo.	No	
mentioned	Not done	Not done	Not done	7 mo.	No	Patient has been off steroids only 3 weeks but remains asymptomatic
spheroidocytes present"	Not done	Pt.—.66 cont.—.80	.32 .32	24 days	No	Patient presented with acute renal failure following artificial renal dialysis. Pt. improved. Urine output returned to normal. Pt. died of overwhelming infection
spheroidocytes"	6.2 micra	Pt.—.66 cont.—.52	.32 .32	30 mo.	Yes	

ries over the last ten years. It should be noted that 9 of the 11 patients presented with spherocytes in the peripheral blood. The occurrence of spherocytes in acquired hemolytic anemias has been discussed by many authors.¹⁻³ However, diagnostic confusion related to this finding continues.

The spherocyte is a cell which has lost its biconcavity; it contains a normal or slightly increased amount of hemoglobin. However, because of its spherical shape, it has a decreased diameter on direct measurement.⁴

Dacie⁵ points out that acquired spherocytes have the same increase in osmotic and mechanical fragility that hereditary spherocytes have. He feels the acquired spherocytosis is due to damage to the cell surfaces. However, as illustrated by the 11 patients presented here, the number of cells which are spherocytic in acquired anemias is seldom great enough to shift the routine laboratory osmotic fragility curve, and the mean red cell diameter (M.C.D.) can vary significantly. Dameshek and associates² first suggested that the macrocytosis which occurs in hemolytic anemia is directly associated with the reticulocytosis seen. This would explain the variation in mean corpuscular diameter from

patient to patient and even in the same patient from one time to another.

It is evident from the above discussion that the morphologic picture expected in acquired and hereditary hemolytic anemias will be the same, and frequently the two are inseparable on that basis alone. However, of the idiopathic acquired hemolytic anemias, therapy is available for only one variety, the Coombs'-positive type. Thus, a positive Coombs' test will not only make the diagnosis but also will suggest an excellent prognosis.

In the published series of uncomplicated Coombs'-positive hemolytic anemia, the mortality rate varies. Since the advent of steroids, the mortality rate has been remarkably low. Litman⁶ lists one death in 13 patients. In our series, there has been one death in 11 patients, and at the time of death that patient's hemolytic component was well controlled.

The therapy of choice has been steroids. Frequently the patients require high doses of steroids to control hemolytic crises and long-term lower doses for maintenance. One of our patients during one severe hemolytic episode required 1,000 mg. of cortisone per day. After three days of this dose, hemolysis was con-

trolled. Steroids were decreased over a period of two weeks to 300 mg. per day. It is our clinical impression that each patient seems to have a therapeutic threshold; when the dose is dropped below that level, a hemolytic episode ensues. Table 1 gives the number of months of therapy required for each patient in our series. It is interesting to note that 4 of the patients were only on steroids a few weeks and their disease has not recurred. Older patients generally have required longer periods of therapy.

Schwartz and Dameshek⁷ have recently published a report on a group of patients with acquired hemolytic anemia that had favorable responses to 6-mercaptopurine. They point out the need for further trials of the drug before it is generally accepted as specific therapy for this disease.

In light of the therapeutic success achieved over the period of time since the introduction of steroids, and considering the possible complications of splenectomy,^{8,9} a simple Coombs' test performed on a patient in whom hemolysis is present with or without spherocytosis may make a diagnosis and suggest more conservative and beneficial therapy.

SUMMARY

The more common findings in acquired hemolytic anemia are briefly described. Special reference is made to the spherocytic nature of the cells in this disease and the ease with which the

diagnosis and therapy are confused by this morphologic finding. A case is presented which illustrates the long-term care necessary to achieve the excellent prognosis which has been our experience at the University of Minnesota hospitals.

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URINARY EXCRETION of the 8 amino acids is increased in children with petit mal epilepsy, possibly because of the disease. In 10 children 10 to 14 years old, amino acid excretion was significantly higher than in 16 healthy children of about the same age. In one patient treated with acetazolamide, complete control of seizures was associated with a change toward normal in excretion of cystine, aspartic acid, glutamic acid, and leucine. Improvement in control of seizures was observed in another patient given a diet low in protein and deficient in cystine.

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Modern Concepts of the Spleen and Anemia

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HISTORICALLY, the spleen has been and still remains controversial regarding the development of anemia. Gretscl,¹ in 1866, was the first to call attention to the occurrence of anemia with splenomegaly. Banti² popularized the concept of splenic anemia. He postulated that either the spleen destroyed large numbers of erythrocytes or that it produced abnormal metabolites which entered the circulation and had secondary effects on the hematopoietic organs. The majority of accumulated evidence supports Banti's former contention.

This review presents the advances in splenic pathophysiology with reference to erythrocyte destruction. Many of these concepts stem from knowledge recently derived from enzymatic and radioisotope studies of normal red cell life spans and changes that occur with various pathologic conditions.

NORMAL AGING PROCESS OF RED CELLS AND THE SPLEEN

Erythrocytes, after a period of one hundred and twenty days, are removed from the general circulation. The erythrocyte death is neither sudden nor unexpected. As erythrocytes age, there is a gradual loss of intracellular enzymatic systems (figure 1). The diminution of glucose-6-phosphate dehydrogenase, methemoglobin reductase, and enzymes of the glycolytic pathway³⁻⁵ indicates decreasing metabolic activity which leaves the older cells in an energy-poor state, incapable of sustaining cellular life.

The spleen has a unique position in determining the period of erythrocyte survival. The red blood cells on their journey through the spleen are subjected to a brief period of stasis. While within the venous sinuses, the plasma is selectively absorbed, and the erythrocytes are left in an environment relatively deficient in necessary nutrients. The older erythrocytes, because of their enzymatic deficiencies, are primarily affected. The period of stasis within the spleen is brief, normally lasting about two to three min-

utes. They are then released into the general circulation where they recover from the metabolic changes. However, a small number of cells, especially those of the older population, cannot recover from the accumulated metabolic insults. These erythrocytes thus become more susceptible to lytic processes and phagocytosis by the reticuloendothelial cells of the spleen and subsequent passages through this organ.

The spleen thus serves not only as a "graveyard" and a "slaughter house" of red cells but it also enhances the "aging" of these cells.

THE SPLEEN AND ABNORMAL AGING OF RED CELLS

Congenital spherocytic anemia. This is an experiment in nature which has presented hematologists with an unusual opportunity to study the pathophysiology of the spleen. It is a hereditary disease transmitted as a mandelian-dominant trait and characterized by anemia, bilirubinemia, a negative Coombs' test, spherocytosis, increased osmotic fragilities, and a positive autohemolysis test.

The autohemolysis test of red cells indicates an abnormal in vitro aging process. This test is performed by incubating red cells in a sterile environment and determining the degree of spontaneous hemolysis. When erythrocytes from a patient with congenital spherocytic anemia are placed into the same testing system, significantly more than normal hemolysis will occur. The degree of hemolysis can be markedly decreased by replacing the supernatant fluid with fresh plasma or by the addition of glucose to the cell suspension. This abnormality is presently believed to be due to a disturbance in carbohydrate metabolism which leads to a slow regeneration of high energy phosphate bonds. From these studies it becomes obvious that although the primary defect is in the erythrocytes, the cell environment is equally important.

The erythrocytes in congenital spherocytic anemia are impeded in their passage through the spleen and consequently are subject to further metabolic injury. Watson and Paine⁶ studied the osmotic fragility of erythrocytes collected either from the splenic vein of patients with

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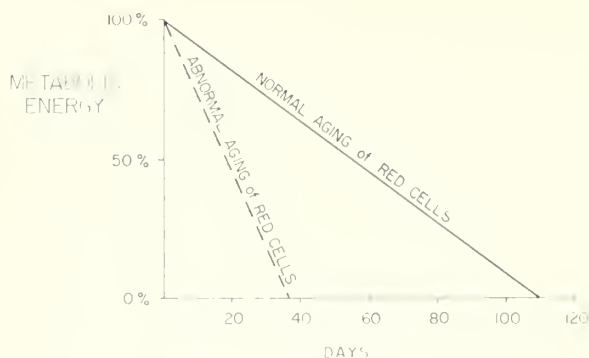


Fig. 1. This schematic representation indicates that concomitant with decrease of metabolic energy, the cell becomes more liable to destruction and cells die. The normal red cell life is approximately one hundred to one hundred twenty days. On the dash line, the abnormal aging of the red cells is noted as a result of decreased metabolic energy. As a result, there is decreased red cell life.

congenital spherocytic anemia after the injection of adrenalin or from the splenic pulp after splenectomy, and they compared them to the osmotic fragility of the peripheral blood. In every instance they were able to show increased osmotic fragility in blood collected from the spleen. Emerson and associates⁷ injected normal, antigenically different erythrocytes into patients with congenital spherocytic anemia prior to splenectomy. After removing the spleen they were able to demonstrate a higher proportion of abnormal cells (spherocytes) with greater abnormalities in osmotic and mechanical fragility within the splenic pulp than were obtained from simultaneous studies of the splenic effluent or the peripheral blood. Further evidence for the accumulation of erythrocytes within these spleens comes from the work of Motulsky and associates.⁸ These workers demonstrated that the hemoglobin content of a normal spleen varies from 11 to 29 mg. per gram of splenic tissue, while patients with congenital spherocytic anemia have 38 to 131 mg. hemoglobin per gram of splenic tissue.

Increased splenic destruction of red cells has been given further confirmation by recent advances in radioisotope technics. After injection of Cr^{51} -tagged congenital spherocytic cells into a normal individual, a marked increase of radioactive counts can be demonstrated over the spleen. This increase in counts is associated with a definitive decrease in red cell survival (figure 2).

Further documentation of the unique role of the spleen is obtained if these same studies are repeated by transfusing Cr^{51} -tagged congenital spherocytic cells into a normal, splenectomized

individual. No decreased cell survival can be demonstrated in this latter case, confirming the importance of an intact spleen for the complete manifestation of the disease.

The increased splenic sequestration that occurs with congenital spherocytic anemia is demonstrated by delayed mixing of tagged cells. The mixing time is defined as the time required for Cr^{51} -tagged cells to reach a constant level in the general circulation. Normally this amounts to two to three minutes, but in patients with congenital spherocytic anemia it approaches forty-five minutes^{8,9} (see figure 3). The fact that the delayed mixing is due to prolonged sequestration of erythrocytes within the spleen is confirmed by delayed equilibration of tagged cells within the general circulation. Complete mixing, therefore, cannot occur until the trapped (sequestered)

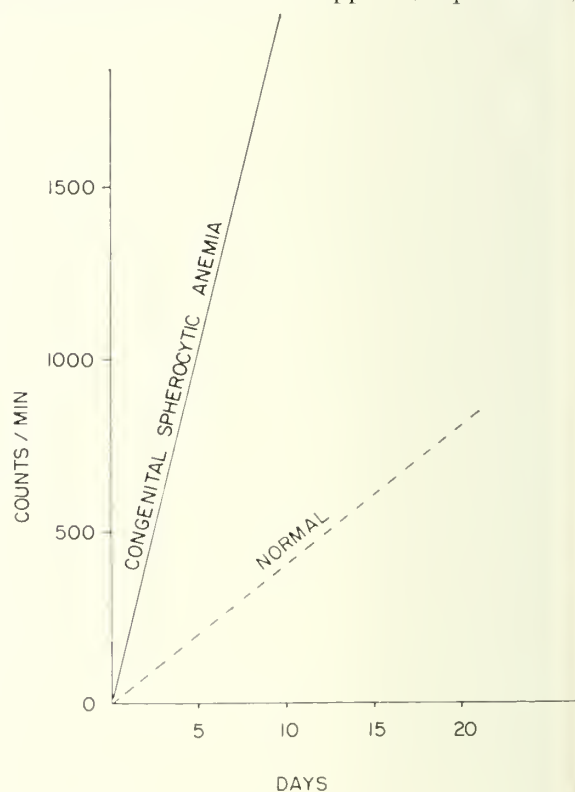
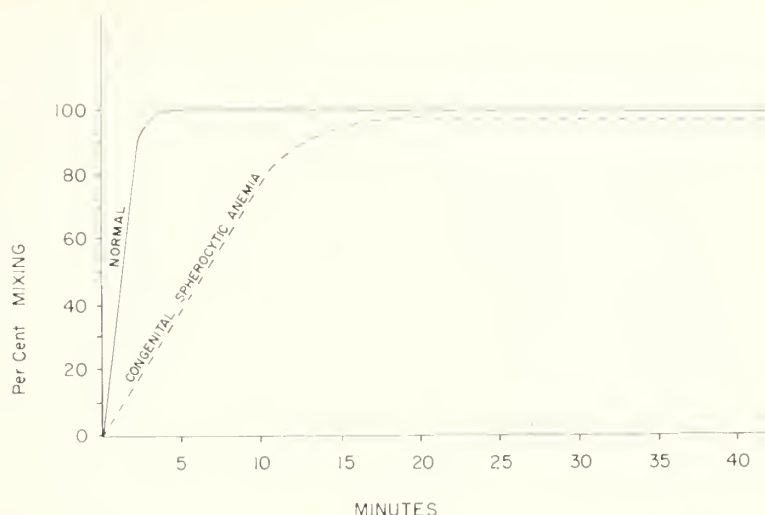


Fig. 2. This is a graphic representation of counts per minute on the ordinate, counted over the spleen, as occurs daily following injection. The straight, unbroken line is a normal. This indicates that counts per minute over the spleen increase only at a slight rate. However, in congenital spherocytic anemia there is a marked increase in the counts per minute over the spleen area. Thus, the counting over the spleen increases proportionally to the amount of sequestration taking place in the spleen. The normal ratio, as obtained by dividing spleen counts by precordial counts, is usually less than 1. If this ratio gets above 2, this would indicate hypersequestration of the red cells in the spleen. These data would indicate that there would be beneficial effect from splenectomy.

Fig. 3. Within a few minutes of injection of radioactive material, the counts obtained from the red cells of peripheral blood increase to 100 per cent of that given. In normal as compared to congenital spherocytic anemia, it can be observed that the normal obtains complete mixing within minutes and the congenital spherocytic anemia obtains complete mixing only after fifteen to twenty minutes.⁸



erythrocytes are released into the general circulation to mix with the tagged cells.

Other workers¹⁰ have demonstrated 2 mixing curves in patients with congenital spherocytic anemia. After a period of two to three minutes following injection of the patient's Cr^{51} -tagged erythrocytes, a constant level of radioactivity develops, indicating complete mixing. Further sampling of the peripheral blood over the next thirty minutes, however, indicates a further decrease of about 10 per cent which usually becomes evident at about seventeen minutes. These observations indicate the presence of 2 distinct erythrocyte pools. The first, characterized by a rapid mixing time, is due to the active peripheral circulation, while the slower mixing time corresponds to the slower blending that occurs within the splenic sinusoids. These authors estimate that the active (fast) circulation of the spleen accounts for one-third of the erythrocyte content of the spleen, and the remaining two-thirds is confined to the sluggish (sinusoidal) splenic circulation.

In summary, there are 2 distinct components in congenital spherocytic anemia: one is the hereditary cellular defect which renders the erythrocytes more susceptible to destruction and the second is the markedly enlarged stasis compartment within the spleen which allows an additional injury to be inflicted on these already damaged cells.

Case history. The following history illustrates the practical application of the above pathophysiology.

B. G. is a 14-year-old white female who was admitted to the University of Minnesota Hospitals in April 1962 for evaluation of anemia. She was apparently in good health until February 1961, when she was admitted to another hospital for an appendectomy. Anemia was noted

at that time and oral iron therapy was instituted. After three months of continuous therapy, the hemoglobin rose to only 11 gm. but later dropped to 9 gm. following discontinuation of the medication. When first seen in our clinic early in April 1962, it was revealed that onset of moderate icterus occurred in the preceding January. Her father was also noted to be icteric; he had splenomegaly but without significant anemia. On physical examination she was found to have moderate scleral icterus and a spleen that was palpable 1 cm. below the left costal margin.

On admission the hemoglobin was 11.9 gm. per cent; marked anisocytosis and spherocytosis were noted on examination of the peripheral smear. The reticulocyte count was 17.5 per cent and the mean corpuscular diameter was 6 micra. Both the direct and indirect Coombs' tests were negative. The total bilirubin was 3.2 mg. per cent. The fecal urobilinogen was 1,456 Ehrlich units (normal upper limits is 350). Examination of the bone marrow showed moderate, increased erythrocyte regeneration. Cr^{51} tagged autogenous cell survival studies indicated a half-life of seven days (normal twenty-five to thirty days) with a splenic-precordial ratio of 2.0 (normal less than 1.5).¹¹ The anemia is thus characterized by marked proliferation, shortened cell survival, and increased splenic sequestration and would probably respond favorably to splenectomy.

Alteration of aging process due to secondary splenomegaly. Anemia has been reported in secondary splenomegaly due to a number of systemic diseases. Yet, the splenomegaly, as such, does not cause the anemia. In polycythemia vera, there is marked splenomegaly due to extramedullary hematopoiesis but no erythrocytosis, as demonstrated by normal mixing times⁸ and absence of decreased survival time. Similar data for fibroadenosis have also been reported.

Recent advances⁸ in radioisotope techniques have greatly aided in our understanding of the basic function of the spleen in the pathogenesis of this type of anemia. Foremost of these is the splenic mixing time, which under normal conditions is two to three minutes. In patients with

secondary splenomegaly, this is increased to about forty-five minutes and represents a marked enlargement of the stasis compartment and resultant hypersequestration. As previously mentioned, this increased stasis deprives the erythrocytes of necessary nutrients for a prolonged period and leads to their premature destruction.

Increased phagocytosis within the hypertrophied reticuloendothelial system of the spleen is also of importance. Studies of the splenic tissue following injections of Cr^{51} -tagged normal cells into individuals with secondary splenomegaly have shown an increased content of this material within the reticuloendothelial system.⁹ Histologic studies of splenic tissue in these conditions have also demonstrated increased intercellular erythrocyte debris within these cells.

Alteration of aging process of red cells due to systemic infection. In a recent report, Jandl and associates¹² presented clinical observations on the alterations in erythrocytes that occur with systemic infections. These workers reported the occurrence of acute hemolytic anemia associated with splenomegaly in 5 patients with acute bacterial and viral infections that could not be explained by any of the usual mechanisms. They were able to demonstrate the presence of a minor erythrocyte population composed of spheroidal cells and increased sequestration over the spleen. The following explanation was offered by these workers: proliferation of the reticuloendothelial tissue occurs with systemic infection and leads to secondary splenomegaly. Hypersequestration and increased stasis develop and lead to metabolic changes in the erythrocytes. The cellular injury is initially reversible, but ultimately it becomes irreversible.

A certain fraction of the erythrocytes, following their release from the spleen, will return, by chance, to this organ while the others will remain in the general circulation and be afforded a period of recovery. In time there will be a minor population of circulating erythrocytes that have undergone repeated erythrocytosis in the spleen without sufficient time in the general cir-

culatation to recover. These cells give evidence of metabolic injury (spheroidal shape) and are in jeopardy of being permanently trapped in the spleen, possibly by virtue of their spheroidal shape.

SUMMARY

The normal function of the spleen in erythrocyte destruction is discussed with particular emphasis on metabolic changes due to aging. The functional importance of the spleen in anemias associated with secondary splenomegaly, infection, and congenital spherocytic anemia are reviewed in light of recent advances in radioisotope techniques.

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Neutropenia in Infancy and Childhood

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ALTHOUGH primary neutropenia is rare in the pediatric age group, during the past few years several etiologically distinct forms have been described. The purpose of this paper is to briefly review some of these of special interest to the physician who cares for infants and children.

NEONATAL NEUTROPENIA

Here we refer to infants who are found to be neutropenic during the first month of life. Because it is not the usual procedure to perform routine white blood cell and differential counts during this period, it is assumed that a diagnosis of neutropenia will probably only be made in symptomatic infants or infants born of mothers whose history included previously affected children. Possible complications of severe neutropenia in this age group include omphalitis, subcutaneous abscesses, skin infections, sepsis, and meningitis. Of course, neutropenia is only a very rare cause of any of these complications. On the other hand, an infant with severe neutropenia will very likely have serious infection, and the infection will be more difficult to treat because of the neutropenia.

INFANTILE GENETIC AGRANULOCYTOSIS

The first clearly defined cause of neutropenia in the neonatal period was described by Kostmann¹ in 1956. He reported 14 cases in 9 families from a single locale in Sweden. All the patients had severe infections, usually starting with subcutaneous abscesses, and only 2 patients survived the first six months of life in spite of antibiotic treatment. White blood cell counts in this group varied from 600 to 6,000 per cubic millimeter and neutrophils varied from complete absence in many to 10 per cent in one case. Some, but not all, of these patients had a peripheral blood monocytosis. Bone marrow studies in all of the patients showed hypercellular marrow with many myeloblasts and promyelocytes but few more mature cells. One patient also had abnormalities of the normoblastic series in the bone

marrow. Peripheral blood hemoglobin and platelets were normal in all his patients. The authors believe this syndrome is due to a genetically determined deficiency in maturation of neutrophil precursor cells.

Case report. This white male child was born five weeks premature by history. The birth weight was 5 lb., 8 oz. At 4 days of age, the child developed a redness around the umbilicus. This was treated with antibiotics, but a swelling that occasionally discharged pus persisted beneath the umbilicus. However, the child took his feedings and gained weight well. At 8 weeks of age, anemia was noted and ferrous sulfate (Fer-In-Sol) was given without effect. At 10 weeks of age, the patient developed a fever and was admitted to a hospital. There white blood cell and differential counts were made for the first time. The patient did not have neutrophils in the blood, and a bone marrow study revealed complete absence of neutrophil precursors.

The patient continued to drain pus from the umbilical mass, and at 6 months of age, surgical removal of the infected urachal duct cyst was attempted. The child had a cardiac arrest when anesthesia was induced. He responded to external cardiac massage, but further surgical attack was not made.

The patient then developed distended superficial abdominal veins and ascites. It was thought that this was due to obstruction of the portal vein by extension of the urachal abscess. The patient died at 8 months of age after three months of continuous hospitalization. In the end he developed a *Pseudomonas* infection with pneumonia and septicemia that did not respond to antibiotic therapy. At no time did he have any neutrophils in his blood or bone marrow. The patient's hemoglobin remained at 10 gm. per cent; his platelet count was normal; the total white blood count remained at about 10,000 per cubic millimeter; and the differential count showed persistent monocytosis (30 per cent) and eosinophilia (20 per cent).

Clinically we believe this case fits the picture described by Kostmann. This patient differs from those described by Kostmann in that neutrophil precursors were not present in the bone marrow.

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It may mean that in this case the genetic defect was at an earlier stage of neutrophil production.

TRANSITORY CONGENITAL NEUTROPENIA

In 1958, Stefanini and associates² described 3 infants born to 2 neutropenic mothers. Peripheral blood counts were done at frequent intervals and in all 3 cases a severe neutropenia was present for the first four weeks of life. The serum of both mothers contained leukocyte agglutinating antibodies, and these antibodies were found in the offspring of one of the mothers. Bone marrow examination showed hyperplasia of the granulocytic series with decrease in mature forms. The cause of neutropenia in these infants is placental transfer of antileukocytic antibodies from the mother. On the same basis, neutropenic infants have also been born to mothers with active lupus erythematosus.³

NEONATAL NEUTROPENIA DUE TO MATERNAL ISOIMMUNIZATION

In 1960, Lalezari and co-workers⁴ described 4 successive children born to a healthy mother, all of whom suffered severe neutropenia for the first ten weeks of life. One became severely infected and died. The mother was shown to have leukocyte agglutinating antibodies directed against the father's and the children's but not her own neutrophils. One of the children had thrombocytopenia as well as neutropenia. Bone marrow showed hyperplasia of the granulocytic series with decrease in mature forms.

Here again, placental transfer of antileukocytic antibodies was implicated in the production of neonatal neutropenia. These cases differ from those described by Stefanini inasmuch as the mother was not neutropenic. This form of neonatal neutropenia is comparable to erythroblastosis fetalis because the mother becomes sensitized to antigens in the fetal cells and not her own.

Treatment of these transferred antibody-induced neutropenias is directed at controlling any infections that may arise. Cortisone has been tried without any effect on the neutrophil count, and in addition, cortisone adds additional risk of infection to an already jeopardized infant. To my knowledge, exchange transfusion has not been done in this disease. Because the disease is self-limited, the conservative approach is probably preferable.

NEUTROPENIA IN INFANCY

In 1956, Stahlie⁵ described a case and reviewed the literature, finding 15 other cases of what he called "chronic benign neutropenia in infancy

and early childhood." These children ranged in age from 6 to 20 months at the time of diagnosis. White blood counts were normal or slightly decreased, and neutrophils were ranged from 0 to 3 per cent of the differential count. Some, but not all, had increased circulating monocytes. These children did not suffer severe infections, although they may have had an increase in minor infections. Bone marrow examinations were normal with the exception of a decrease in mature granulocytes. Twelve of the 16 patients recovered within one year, 2 patients recovered between two and four years, and 2 patients continued to have neutropenia one year after diagnosis when the report was made. Only 1 of the 16 patients died. The cause of this benign form of neutropenia is not known.

Case report. This white female was first seen at the University of Minnesota Hospitals at 8 years of age because of a persistently low white blood cell count. The patient's history included treatment for meningitis at the age of 1 year. Her white blood cell count at that time was 15,000 per cubic millimeter with 95 per cent neutrophils. In the next six years the patient had several episodes of bronchitis and possibly pneumonia, but she did not require hospitalization. At 7 years of age she was hospitalized for pneumonia, and a low white blood cell count was found. At 8 years of age, on admission to the University of Minnesota Hospitals, the patient was of normal size, she was well nourished, and the only physical finding of note was the enlargement of the anterior cervical lymph nodes. Laboratory work revealed a hemoglobin of 14.1 gm. per cent, platelet count of 210,000 per cubic millimeter, and a white blood cell count of 1,750 per cubic millimeter, with 28 per cent neutrophils, 65 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils, and 2 per cent basophils. Bone marrow revealed a hyperplastic marrow with many neutrophil precursors.

The patient has been observed for three years, and during this time she has had a persistent leukopenia, usually below 1,000 total cells. Her neutrophils have numbered about 30 per cent of the total. On 2 occasions when the patient developed bacterial infections, the white blood cell count rose to nearly normal levels and a neutrophilia was actually present. During this period of observation without any therapy, the patient has not shown any increased susceptibility to infection.

Although this patient is older than individuals in the group described by Stahlie, the benign cause of her disease seems to place her in this group.

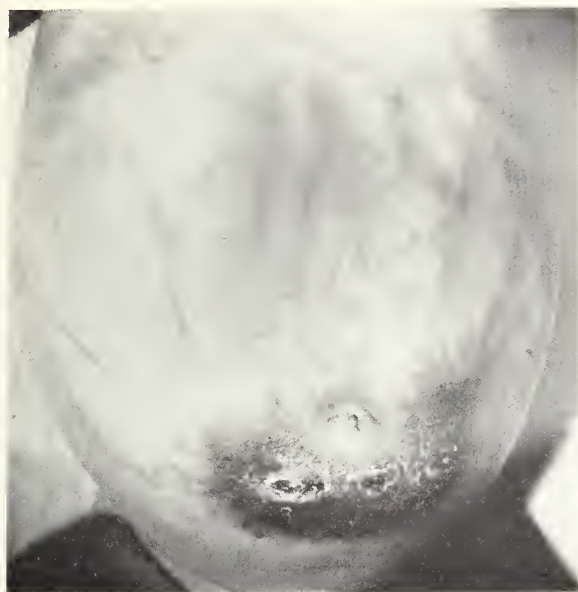


Fig. 1. A 6-month-old infant with congenital neutropenia, showing the infected umbilical cyst and distended superficial abdominal veins

NEUTROPENIAS OF CHILDHOOD

Cyclic neutropenia. This disease is characterized by regular cyclic fluctuations in the neutrophil count. In most cases the cycle repeats itself every twenty-one days, but a few cases with cycles of fourteen-day intervals have been described. The neutrophil count ranges from 0 at the low point to nearly normal at the high point. The white blood cell count remains stationary and a monocytosis regularly occurs during the neutropenic phase of the cycle. During the neutropenic phase, the patients often acquire infections such as otitis media, paronychia, or abscesses. The neutropenic phase is usually accompanied by fever, malaise, and ulcers of the buccal mucosa. It is of interest that cortisone treatment will abolish the fever, malaise, and buccal mucosa ulcers without changing the neutrophil count. Evidence is now accumulating that this disease is inherited, probably as a dominant trait. As the patients become older, they often stop having symptoms with their periods of neutropenia, although the blood cycle is unaltered. Bone marrow studies have shown that all the neutrophil precursor cells participate in the cyclic phenomenon (see figure 1).⁶

Splenectomy has been tried as a therapeutic measure, but it is ineffective and, on the basis of our experience in one case, improper. One of our patients had repeated episodes of minor infections until splenectomy was done at 15 years of age. During the following three years, she

had several attacks of pneumonia and developed lung abscesses on 3 occasions. Three other patients we have studied have had only minor infections.

Neutropenia and agammaglobulinemia. Approximately 20 per cent of the patients with congenital agammaglobulinemia whom we have studied have had one or more episodes of severe neutropenia. These are almost always associated with infection, and usually the blood count returns to normal after the infection has cleared up. Although several of the patients have had repeated episodes of neutropenia, there is no regular periodicity to the episodes as there is in cyclic neutropenia. Because of this association, it is worthwhile to check the gammaglobulin level on any patient with neutropenia. Good⁷ explains the occurrence of neutropenia in agammaglobulinemia patients on the basis that both agammaglobulinemia and neutropenia are manifestations of an abnormality in the primitive reticulum.

Primary splenic neutropenia. In 1942, Wiseman and Doan⁸ described a series of patients with neutropenia, enlargement of the spleen, and hyperplasia of the granulocytic series in the bone marrow. The neutropenia in these patients responded to splenectomy. Some of these patients also had thrombocytopenia and hemolytic anemia.

Demonstration of antibodies directed against red cells and platelets as a probable cause of hemolytic anemia and thrombocytopenia started people searching for white blood cell antibodies to explain primary neutropenias. Moeschlin⁹ was able to produce leukopenia in normal subjects by injections of serum from a patient with agranulocytosis. This remains the most convincing evidence yet presented that antibodies can produce neutropenia.

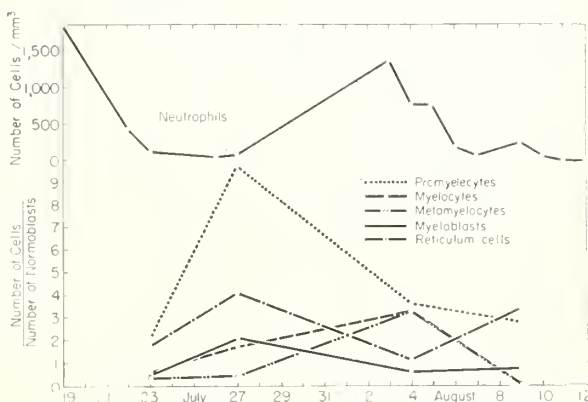


Fig. 2. Graphic illustration showing the cyclic fluctuations of the neutrophil precursor cells located in the bone marrow of a cyclic neutropenic patient

Dausset¹⁰ has done extensive work trying to demonstrate antileukocytic antibodies, and with his most recent direct antiglobulin consumption test, he can show gammaglobulin attached to the leukocytes of about 50 per cent of patients with idiopathic neutropenia. It appears that antileukocytic antibodies are associated with many cases of splenic neutropenia, but how frequently the antibodies actually contribute to the production of neutropenia is not known.

DRUG-INDUCED NEUTROPENIA

Children, as well as adults, may develop agranulocytosis when exposed to toxic compounds. Drugs may act to produce agranulocytosis either by a direct toxic action on the bone marrow as in the case of chloramphenicol (Chloromycetin) and chlorpromazine¹¹ toxicity or, as in the classical aminopyrine-induced agranulocytosis, the drug may act as a haptene and induce antibody production against a combination of drug and white blood cell.¹² Of course, the treatment of drug-induced agranulocytosis is withdrawal of the offending agent and protective isolation of the patient.

NEUTROPENIA SECONDARY TO SYSTEMIC DISEASE

Although the purpose of this paper is to review the primary neutropenias, I should point out that neutropenia is more often a sign of some systemic disease. In most cases, the disease causing the neutropenia is obvious, as in patients with leukemia and malignancies that cause neutropenia by replacement of bone marrow. Anemia and thrombocytopenia are also usually present in these cases.

Neutropenias may be due to excessive destruction of neutrophils by an enlarged spleen. Here again, thrombocytopenia and hemolytic anemia are often present. Splenic enlargement may be secondary to portal hypertension in patients with intra- or extrahepatic portal vein obstruction, or it may be due to an infiltration process in the spleen, as seen in histiocytosis and Hodgkin's disease.

The presence of neutropenia in a patient with polyarthritis may be a helpful initial clue in making the diagnosis of lupus erythematosus, as both rheumatic fever and juvenile rheumatoid arthritis are associated with neutrophilia.

RESISTANCE TO INFECTION

Studies of the inflammatory response show that neutrophils are the body's first line of defense against bacterial invasion. In addition to acting as phagocytes and killing bacteria, the neutrophil stimulates the migration of lymphocytes from the blood vessels into the site of inflammation.¹³ In an animal or patient with complete neutropenia and a normal lymphocyte count, the appearance of the lymphocytes at the inflammatory site is delayed by several hours. As a result, the patient with complete neutropenia is in double jeopardy. Fortunately, only a few neutrophils are necessary to stimulate lymphocyte migration. Patients with as few as 3 to 4 per cent neutrophils and a normal white blood cell count are able to mobilize their lymphocytes normally. In view of the importance of the neutrophil as a defense against infection, it is surprising that patients with neutropenia do not have more difficulties than they do. With the exception of the newborn period, neutropenic patients seem to be bothered mostly by minor infections. In patients with cyclic neutropenia, monocytes may take over the neutrophils' role as the first line of defense. However, patients such as our second case who are leukopenic and neutropenic are difficult to explain. It may be that patients such as this one are able to respond to infection with an outpouring of cells from the already hyperplastic marrow. As the cells would be rapidly used up at the site of infection, no increase in peripheral blood cells would necessarily be noted. This might explain the difference between the resistance of patients with benign neutropenia and the extreme susceptibility to serious infection seen in patients with drug-induced agranulocytosis and in patients with leukemia, both being instances where the bone marrow may be unable to respond.

The serious nature of neutropenia in early infancy may be related to other unknown factors that make the newborn susceptible to infection.

SUMMARY

An attempt has been made to briefly review some of the syndromes associated with primary neutropenia in infants and children.

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DISLOCATION of tarsometatarsal joints is best treated by closed reduction. Chances of restoring joint stability are good provided an initial, exact anatomic reduction is achieved and maintained. When closed reduction is unsuccessful, open reduction and fusion should be done. However, early surgery is inadvisable if there are unstable fractures of the metatarsal shafts or other foot damage. The tarsometatarsal joints have only an insignificant degree of mobility, so little attention is given to future mobility of these joints.

W. M. GRANBERRY and P. R. LIPSCOMB: Dislocation of tarsometatarsal joints. *Surg., Gynec. & Obst.* 114:467-469, 1962.

FOCAL SEIZURES may be the first sign of intracranial tumor in children. They are most common with slow-growing and relatively benign lesions. Early diagnosis allows surgical removal with good prognosis. The seizures are more common with supratentorial tumors than with infratentorial ones. Their pattern often pinpoints location of the tumor, but an electroencephalographic record is more reliable. Children with cryptogenic seizures require neurologic examinations for many years. Focal seizures alone do not dictate neurosurgical diagnostic procedures. Other factors must be considered.

R. E. BACKUS and J. G. MILLICHAP: The seizure as a manifestation of intracranial tumor in childhood. *Pediatrics* 29:978-984, 1962.

WORK CAPACITY of patients after myocardial infarction can be evaluated by a 5-stage test using facilities available at occupational therapy clinics. Cardiovascular and general responses to test movements indicate readiness for self-care, light industrial tasks, or sedentary industrial or office work. During the 5 stages, which range from light hand activity to lifting a 10-lb. weight, oxygen consumption, pulse rate, arteriovenous oxygen difference, effective arterial blood pressure, electrocardiographic changes, and cardiac output and work are monitored.

F. J. KOTTKE, W. G. KUBICEK, MILDRED OLSON, RUTH H. HASTINGS, and KARYNE QUAST: Five stage test of cardiac performance during occupational activity. *Arch. Phys. Med.* 43:228-234, 1962.

Melena Neonatorum

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MELENA in its more specific sense means a black, tarry stooling indicating the presence of degraded blood in the gastrointestinal (GI) tract. However, through common usage it has been broadened in its meaning as applied to the neonatal period to include the presence of any blood in the stool. In this discussion we will consider briefly nearly all sources of blood in the neonatal stool, as outlined in the table. In addition, hemorrhagic disease of the newborn will be discussed more extensively since this problem seems to be associated with a good deal of confusion both in the literature and in the mind of the clinician.

It is worth noting here that due to the rapid transit time of the GI tract in the neonatal period, blood from any source, including swallowed blood, may be passed in the stool as bright red blood. Therefore, while as a general rule darker color indicates longer presence in the GI tract and thus a higher source of blood, in the neonatal period the passage of red blood in the stool does not exclude any level of the GI tract as a source of the blood.

In dealing with the problem of melena in the newborn infant, the clinician must make every reasonable effort to find the source of bleeding. However, he must keep in mind that "in an astounding proportion of patients the cause of bleeding is never found."¹

RELATIVELY BENIGN SOURCES OF STOOL BLOOD

There are several sources of stool blood in the neonatal period which can be considered relatively benign since they represent sources which are of little consequence to the infant's well-being. These require little, if any, treatment and will usually clear spontaneously. Swallowed blood, either maternal or the infant's, is a rather frequent such benign source. Maternal blood may be swallowed at the time of delivery or may be from nipple or breast lesions if the child is breast-fed. The infant may incur minor sources

of nasal or oral bleeding from the trauma of delivery, such as the use of forceps, or from overly vigorous resuscitation procedures and thus swallow his own blood. The simple test devised by Apt and Downey² may be used to differentiate between infant and maternal blood.³ A fissure of the anus or trauma in the anal area due to insertion of a thermometer or wiping in diaper change may also be causes of a bloody stool. It should be kept in mind that blood on the stool of a female infant may represent the normal vaginal bleeding seen in about 5 per cent of female newborns on the third or fourth day of life secondary to hormone withdrawal.

ABNORMALITIES LOCALIZED TO THE GI TRACT

Under this heading of the outline are listed those conditions which represent abnormalities confined to the gastrointestinal tract. In the preceding benign conditions, the presence of blood in the stool is usually an isolated finding. While this may also be true of this group, for the most part there will be accompanying signs such as diarrhea, vomiting, pain, or an acute abdomen.

Any of the usual enteric pathogens, either viral or bacterial, may be responsible for a gastroenteritis of the newborn period. In addition to the usual organisms, *Monilia* and the Friedlander's bacillus have been found to cause bloody diarrheas in the newborn.

Duplications may occur as anomalies of any portion of the GI tract. These frequently produce areas of necrosis by their pressure upon the nutrient blood supply.¹ Bleeding from the duplication or adjacent areas of the GI tract may also be from ulceration produced by the secretions of ectopic gastric mucosa which is frequently found in these duplicated segments. Ectopic gastric mucosa as a source of bleeding may also be present in an otherwise normal bowel segment or in a Meckel's diverticulum.

³One part of the bloody stool is mixed with 5 to 10 parts of tap water to lyse the red cells and give a pink hemoglobin solution. This is centrifuged and filtered. To 5 ml. of this solution is added 1 ml. of 0.25 N sodium hydroxide. Adult hemoglobin will show a pink to brown color change in two minutes, while fetal hemoglobin remains unaltered.

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TABLE

AN OUTLINE OF CONDITIONS WHICH MAY BE ASSOCIATED WITH THE PRESENCE OF BLOOD IN THE STOOL OF THE INFANT IN THE NEONATAL PERIOD

- I. Relatively benign sources of stool blood
 - A. Swallowed maternal blood
 - B. Swallowed infant blood
 - C. Minor ano-rectal bleeding.
- II. Abnormalities localized to the GI tract
 - A. Gastroenteritis
 - B. Duplications of the GI tract
 - C. Ectopic gastric mucosa
 - D. Esophagitis and esophageal ulceration
 - E. Uleers of the stomach or duodenum
 - F. Rupture of the stomach or small bowel
 - G. Partial obstructions
 - H. Meckel's diverticulum
 - I. Intussusception
 - J. Primary mesenteric artery thrombosis
 - K. Ulcerative colitis
 - L. Bowel polyps, hemangiomas, teratoma
 - M. Cow's milk allergy
- III. Coagulation abnormalities
 - A. Thrombocytopenias
 - B. Fibrinogen deficiencies
 - C. Deficiencies of clotting factors not responsive to vitamin K
- IV. Hemorrhagic disease of newborn

Ectopic pancreas has also been found in the wall of the gut and may be the source of bleeding into the GI tract.³

A rather frequent source of localized GI bleeding is esophagitis or esophageal ulcer. These may be associated with a congenital hiatus hernia or with repeated regurgitation secondary to chalasia or obstruction of the GI tract below. Esophagitis with bleeding may also be caused by a moniliasis.⁴

True peptic ulcers of the newborn period are quite rare, with only about 300 having been reported in either the stomach or duodenum. A relatively more common source of bleeding is the stress ulcer seen as a secondary complication of brain damage, such as with subdural hematoma or central nervous system hemorrhage.⁵ Frequent regurgitation of small bowel contents into the stomach as a result of obstruction may also produce ulceration of the gastric mucosa and bleeding. Perforations of the stomach may occur due to such ulceration, but a few have also been found where there was no associated ulcer on trauma. It is believed by some that a congenital muscle defect in the upper anterior surface of the stomach exists where most of these latter perforations occur. Small bowel ruptures have also been reported and are usually secondary to obstruction or trauma.

There are several causes of GI tract obstruction in the newborn. Of course, for an obstruction to allow the passage of blood by way of the rectum it must be a partial or intermittent obstruction. Some of the conditions which may produce such an obstruction are hypertrophic stenosis of the pylorus (or rarely hypertrophic stenosis of the duodenum), duodenal stenosis, annular pancreas, restricting peritoneal bands, or aberrant vessels such as the superior mesenteric artery. These bands or obstructing vessels may occur alone or in association with malrotation of the gut. Malrotation may also produce partial or complete obstructions by a volvulus or by cecal pressure on the small bowel.

One of the more frequent sources of melena neonatorum is a Meckel's diverticulum. This structure may be torn or ruptured by the trauma of birth or it may be the lead structure in the formation of an intussusception. However, intussusceptions are very rare in the newborn period. Less than three dozen cases have been reported under 3 months of age.³

Allergy to cow's milk usually presents in the newborn period and is associated with colic, vomiting, and bloody mucoid stooling.

Two very rare causes of melena in the newborn are a primary thrombosis of a mesenteric artery and ulcerative colitis. The cause for thrombosis of a mesenteric artery, which results in necrosis and bleeding, is unknown. Only 3 cases of ulcerative colitis in the newborn period have been reported.^{1,6-7} Three other entities which may cause gastrointestinal bleeding but have not yet been found in the neonatal period are bowel polyps, hemangioma of the bowel wall, and a teratoma in contact with the bowel lumen. All of these have been found as causes of bleeding in the GI tract shortly after the newborn period and probably exist, but have not yet been diagnosed, in the neonate. Hemangiomas of the bowel wall as a source of melena are frequently mentioned, but to date there are only 15 reported cases under 16 years, the youngest being 2 months of age at diagnosis.⁸

COAGULATION ABNORMALITIES

There are several conditions commonly associated with rectal bleeding in the newborn which are not localized to the GI tract. Most of these cause bleeding because of their effect on the clotting mechanism of the blood. These are found listed in the last 2 sections of the outline in the table.

In evaluating any bleeding problem in the newborn, the blood platelet count must be investigated since there are many possible causes

of a thrombocytopenia in the newborn. Many infections such as cytoplasmic inclusion disease, toxoplasmosis, torulosis, herpes simplex, congenital syphilis, and pseudomonas sepsis may lower the platelet level.⁹

Maternal antibodies against the infant's platelets may be transferred from the mother with idiopathic thrombocytopenic purpura even if she is asymptomatic at the time.⁹ However, the condition is usually asymptomatic and self-limited. Supportive therapy is needed only when definite signs and symptoms are present. Exchange transfusion with fresh blood to restore adequate platelet levels and adrenocorticotrophic hormone or cortisone have been used.¹⁰

There may also be iso-immunization of the platelets without the presence of purpuric disease in the mother. She may also be sensitized by drugs such as quinine, sulfonamides, or other quinone derivatives. Two cases have been reported where the maternal antibodies were directed against the megakaryocytes rather than the peripheral platelets, causing a marked depression of the bone marrow.¹¹ It should be cautioned that breast feeding is to be avoided in any situation where maternal antibodies are suspected, since the antibodies may also be transferred to the infant in the milk.

Inadequate storage of blood used in exchange transfusion may destroy the platelets and result in a thrombocytopenia in the recipient of the blood.

Peripheral destruction of the platelets may be due to congenital idiopathic thrombocytopenic purpura or familial purpura of the type associated with otitis and eczema (Aldrich syndrome). The platelets also may be destroyed by sequestration in giant hemangiomas but will return to normal levels with the destruction of the hemangioma by roentgenization or surgical removal.¹²

Bleeding may also be secondary to a fibrinogen deficiency.⁹ Congenital afibrinogenemia is caused by a very rare autosomal recessive and is characterized by umbilical and GI bleeding; it may or may not have an associated thrombocytopenia. In these patients there are no detectable blood fibrinogen levels, and they must be maintained by blood or plasma or commercial fibrinogen preparations. Five patients have been reported in whom there are low but detectable levels of fibrinogen, and these have been termed constitutional hypofibrinogenemias. Severe liver disease such as neonatal hepatitis may decrease the production of fibrinogen sufficiently to allow bleeding. In such instances, there is usually a decrease in the prothrombin level as well. Neither of these deficiencies will respond to vitamin

K in the presence of the severe hepatic disease. Intravascular clotting with utilization of the fibrinogen has also been reported. The presence of pathologic amounts of circulating fibrinolysins has been postulated, but no evidence of these in the newborn period has been found.

Congenital deficiencies of some of the other coagulation factors which may occur, but are very rare in the newborn, are antihemophilic globulin (hemophilia), labile or stable factor deficiencies, or a congenital enzymatic inability to synthesize prothrombin. None of these genetic disorders will respond to the administration of vitamin K.

HEMORRHAGIC DISEASE OF THE NEWBORN

A rather infrequent cause of neonatal bleeding which has received a good deal of recent comment and discussion is hemorrhagic disease of the newborn. This entity was first described by Townsend¹³ in 1891 when he reported on 50 cases of spontaneous bleeding occurring usually on the second or third day of life and differing from classical hemophilia in its self-limited nature and a lack of familial bleeding history. At that time, little was known of the mechanism of blood coagulation, and Townsend felt that the etiology was probably infectious. No doubt many conditions were originally included under this title which, through increased understanding of the involved physiology, are now classified elsewhere. The future will probably bring further refinement of the concept of this disorder. However, at the present time, hemorrhagic disease of the newborn can be considered as any bleeding seen in the newborn period as a result of deficiencies of clotting factors whose synthesis is dependent upon vitamin K. This is by no means a firm and generally accepted definition since there are authors who still include under this heading all neonatal bleeding not otherwise readily explained. In fact, one author has even included the normal vaginal bleeding of hormone withdrawal in his incidence statistics. It is this variation of definition from one author to another which is in a large part responsible for the widely varying figures of general incidence of hemorrhagic disease of the newborn. The highest incidence, as reported by Jenny and Gschwend,¹⁴ was 3.2 per cent, while Potter,¹⁵ whose series included 13,000 infants from the Chicago Lying-In Hospital, found only 2 probable cases of hemorrhagic disease of the newborn. Aballi and his group¹⁶ at Charity Hospital in Havana found 26 cases, or an incidence of 1 in 300 deliveries.

In the normal newborn infant, the levels of

the 4 factors of coagulation which are dependent upon vitamin K are reduced from the adult normals.¹⁷ These factors are prothrombin (factor II), Stuart factor (factor X), stable factor (factor VII), and plasma thromboplastin component (factor IX) (see figure). One factor, proaccelerin or labile factor, is present at levels above adult normal and may in part compensate for the deficiencies in the vitamin K dependent factors. All other factors are at normal or near normal levels in the newborn infant.

Prothrombin time, which indicates the adequacy of the second phase of coagulation as shown in the figure, has been studied in the newborn by several authors. The prothrombin activity (done by Quick's 1-stage method) immediately after delivery is found to be normal. However, there is a decline in the prothrombin activity over the next several hours following birth, reaching its lowest levels on the second or third day of life. In most infants, this lowest level is still adequate to prevent a hemorrhagic diathesis. In perhaps 1 newborn in 20, this drop reaches levels which may allow overt hemorrhage. After reaching its lowest point on the second or third day, the prothrombin activity slowly increases over the following months, reaching adult levels about the end of the first year.

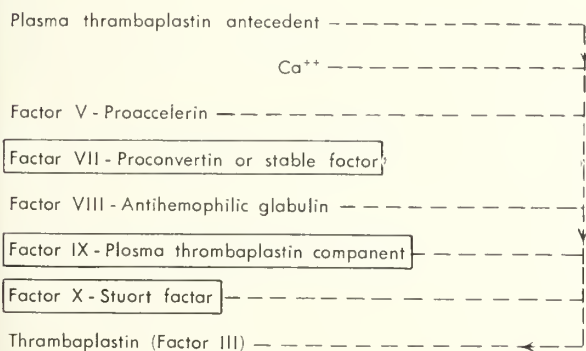
In those infants who show a marked prolonga-

tion of prothrombin time, the administration of 2 mg. of intramuscular vitamin K usually raises the prothrombin activity to about 25 per cent of adult normal within four to six hours. This level is quite adequate to maintain hemostasis. Obviously then, vitamin K is the specific treatment indicated for bleeding in the newborn in the presence of a marked depression of prothrombin activity. Usually these infants will also require supportive measures such as transfusion. In most instances plasma or stored blood is adequate, since all the vitamin K dependent factors are stable.

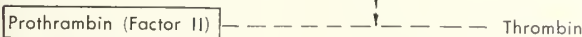
Prophylactic use of vitamin K. The restorative effect of vitamin K upon the prothrombin activity has led to its administration either to the mother prior to delivery or to the infant as a prophylaxis against hemorrhagic disease in the newborn. The efficacy of this prophylaxis has been the subject of several studies which have led to wide disagreement as to its usefulness. Vietti, Stephens, and Bennett¹⁸ studied approximately 200 infants and mothers who were divided into 4 groups. In the first group, only the mothers were given vitamin K in doses of 5 mg. daily for one month prior to delivery. In a second group, only the infants received vitamin K as a single 5 mg. injection on the first day of life. The infants in these 2 groups experienced no bleeding and had near normal prothrombin times. No vitamin K was given to either the mothers or the infants in the control group, and of these 50 infants, 14 had prolonged prothrombin times and 4 bled. This and similar studies giving evidence in support of the use of prophylactic vitamin K in the newborn must be contrasted with other studies which show neither alteration of the mortality rate nor the incidence of neonatal hemorrhage.

A comparison of the studies in the literature in regard to both the prophylactic effect of vitamin K and the incidence of hemorrhagic disease in the newborn must lead one to conclude that other unmeasured factors are involved. One of the highest incidences reported was among a very low socio-economic group suggesting the probable importance of maternal prenatal dietary factors.¹⁶ The presence of higher levels of vitamin K in cow's milk than in breast milk and the time of the first milk feeding after delivery will have their influence upon this problem. It has been observed that the incidence of neonatal hemorrhage is greatest in early spring and lowest in the fall. Such climatologic, dietary, and possible hereditary factors have not been adequately evaluated. However, based on the information available, it seems advisable to pro-

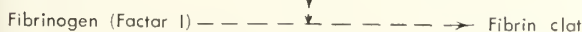
Phase I.



Phase II.



Phase III.



A schematic representation of the clotting mechanism. Those factors which are dependent upon vitamin K for their production are enclosed. (Stable factor is not necessary for the completion of phase I under ordinary circumstances.)

vide adequate prenatal vitamin K for the mother or to administer a single intramuscular dose of vitamin K to the infant in the first day of life. Because of the hyperbilirubinemic effect reported for some of the synthetic vitamin K analogs, high doses of these drugs should be avoided.¹⁹ The Council on Drugs of the American Medical Association recommends the use of 1 mg. menadione or its equivalent and states that up to 5 mg. may be considered safe.²⁰

SUMMARY

It has been the endeavor in this article to review briefly the many possible causes of melena neonatorum, which was defined as the passage of any blood through the rectum in the newborn period. Greatest emphasis has been placed upon hemorrhagic disease of the newborn, including the present recommendations regarding the prophylactic use of vitamin K in the newborn.

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CYCLIC PAIN related to the menstrual period identifies endometriosis of the sciatic nerve. It becomes constant if the endometriosis is not treated. Peritoneal evagination by intrapelvic endometrium to form a pocket in continuous retroperitoneal tissues helps to locate the hidden lesions. In most instances, only limited resection of affected tissue is possible. Castration by irradiation is the best treatment.

H. B. HEAD, J. S. WELCH, ELIZABETH MUSSEY, and R. E. ESPINOSA: Cyclic sciatica. *J.A.M.A.* 180:521-524, 1962.



Notes from a Medical Journey

Corfu, Greece
24 September, 1961

Dear Jay:

This bedroom in the "Castello" near the town of Corfu is a far cry from the Tiflis-Moscow plane. I estimate the ceiling is 20 feet up and I paced the floor to yield an estimate of 25 feet square. Windows look out on pines and enormous pyramidal cypresses in gardens and then olive groves sloping down to the Ionian Sea, with a view across it of the desolate mountains of Albania only a couple of miles away.

By the time this letter is finished my colleagues should be returning from their work examining the men of the nearby villages. Then I'll put on bathing trunks and we'll walk down to the beach for a swim in crystal clear and very salty water. Margaret, Professor Noboru Kimura of Japan, Dr. Branca Tiefenbach of Zagreb, Yugoslavia, and a bright Greek doctor with the difficult name of Stamatoyannopoulos should join us too. They must finish the immunochemical measurements of beta lipoprotein in the day's batch of about 40 blood samples. This new method works with great dispatch -- we ran 72 samples, in duplicate, in our first routine afternoon's work with only half a dozen needing to be repeated because of poor checks.

Incidentally, all the way from Minnesota we have carted 47 pounds of centrifuge, etc., plus 2 thermos flasks, for the lipoprotein method but it has been well worth it. Margaret demonstrated the method with great success in Brussels and in Russia before we got here. Doctors Myasnikov and Kipshidze were much interested and I hope to enable them to put the method to use in their institutes. The only technical snag was in Russia where we had to rig up alcohol lamps to seal the glass capillaries. Both in Moscow and in Tiflis we could not use Bunsen burners because "temporarily" there was no gas in the lines. Here in Corfu we use a little butane torch.

Now about Sukhumi in Georgia, on the eastern shore of the Black Sea. Sukhumi, Sotchi, and a hundred miles of coast between are largely given over to resort hotels, where many thousands of Russians take their vaca-

tions, free or at small cost. The scenery is wonderful and the climate is mild all year. All over Russia people at every level of society try to get their reward of an annual trip to the Black Sea.

But our interest in Sukhumi was in the monkey colony and in the old men of the mountains. The monkey colony, as a center for research, goes back a long time but the present vigorous program began a dozen years ago. Various species are under study, but baboons, some being the eighth generation born there, are in the majority among the 1,300 monkeys in the colony. Deaths exceed births, but the population is kept up by imports from India and Africa.

Most of the research is done by the resident staff (Prof. Panin, director) but visiting researchers from other places in Russia are numerous. There are active programs in virology, endocrinology, and various diseases but of course we were most interested in the work on hypertension and atherosclerosis. Little or no work on nutrition has been done, and I was unable to get details of the chemical composition of the stock diet (which has been arrived at by trial and error) but it is clearly low in fat.

Baboons live in a family of a "head man," 20 to 30 females, and the offspring up to an age of about 2 years. At this age the young males must be segregated to prevent constant warfare. The most important experiment has been to "dethrone" the head man, putting him in a separate cage within his domain, and to introduce other adult males to take over. In a few weeks the dethroned male is apt to have constant hypertension, and in some cases, after months of this "stress," the electrocardiograph indicates coronary insufficiency or infarction. At autopsy, definite myocardial infarction was found in half a dozen cases.

Quantitative studies on the arteries are lacking, but the photos I saw of specimens did not show striking degrees of atherosclerosis. I did not see any data on the blood. I suggested that atherogenic diets be tried and was told that such experiments are planned.

Not far from Sukhumi is an area of farmer-shepherds, a sort of transition between pastoral and settled agricultural life. We were told that in this small region there are more than 300 men over 100 years of age. Anyway, we spent a hilarious afternoon at one of the farms with an old man of 117, his eighth wife, his "kid brother" of 96, his youngest son aged 23, and a flock of relatives and neighbors.

Ages are from church parish registries and tax records. It does seem that the old man has been around a long time; in 1884 he built his present farmhouse. Anyway, there was a great feast with innumerable toasts in wine. Dr. Paul White and his "older brother," as he called the old man, drank two "bottoms up" in vodka, whereupon old 117 tried to teach "younger brother" Paul (aged only 75) a Caucasian dance. Then the oldster called for his horse and trotted around making war whoops in the rain while we all howled with laughter.

The oldest man at the party was a neighbor, aged 126, who walks a mile and a half daily to call on his old pal. Old 126 was a bit creaky, slightly deaf, and probably half blind. At the long meal he went to sleep frequently, but only for a couple of minutes. Then, eyes closed, he would fish out tobacco and paper and roll a cigarette. Someone would give him a light and then he would reach out for a glass of wine. What a day!

Dr. Kipshidze and colleagues want to organize a systematic study of people in these parts and have agreed to follow my protocols and methods, just as used here in Corfu. I suggested they study all the men over 90 and random samples of about 50 men in each decade from ages 20 to 90. There is a chance that we may go there again next July to help organize and standardize a survey. Also, I want to get more details about the diet which is obviously very low in animal fat. A main staple at every meal is a great dish of white corn meal mush. Where can I find a dietitian who speaks Georgian and Russian (unrelated)?

But now it is time to swim. Doctors C. Aravanis, A. S. Dontas, D. Lekos, and company have organized the job here so well that the main work of the day (starting before 8 a.m.) is finished by midafternoon, except for Miss Sdrin and her four dietitians who have no break checking the foods as eaten in the homes. After the swim and before dinner (usually about 9 p.m.) Dr. Ivan Mohacek (of Zagreb) and others will reread and classify the electrocardiograms of the day.

At this rate the whole job (700 subjects) will be done in less than a month. Margaret and I must leave tomorrow for Italy if we are to finish there and get home in ten days.

All the best,

As ever,



Ancel Keys

AK/ji



Chauncey A. McKinlay, M.D.

RUTH E. BOYNTON, M.D.

Miami, Florida

CHAUNCEY A. MCKINLAY was born August 9, 1890, in the State of Kansas. His father and mother, Lincoln McKinlay and Jennie Knickerbocker McKinlay were both rural school teachers. Having been brought up in a family of educators, it is not surprising that Chauncey McKinlay, although his life has been spent in the private practice of medicine, has always been interested in teaching young physicians with whom he has been associated.

His father, Lincoln McKinlay, was at one time superintendent of schools in Haskell County, Kansas, and also was a country newspaper editor in Newkirk, Oklahoma. He served as the first president of the Oklahoma Historical Society.

Among his early memories, Chauncey McKinlay recalls standing, as a 10-year-old boy, at the periphery of a small crowd on the end platform of a Santa Fe train listening to Theodore Roosevelt give a speech in his campaign for vice president in 1900. Roosevelt's running mate for the presidency was William B. McKinley. Dr. McKinlay recalls that in 1901 the McKinlay family stood in the music hall of the Buffalo Exposition in Buffalo, New York, where a week later William B. McKinley was shot and became the third martyred President of the United States. President McKinley's great grandfather and Dr. McKinlay's great, great grandfather were brothers.

Dr. McKinlay attended high school in Newkirk, Oklahoma, and was graduated from the

Wichita, Kansas, High School in 1908. For the next two years he attended Fairmont College, now Wichita University, and then transferred to Kansas University where he received a B.A. degree in 1914. In 1916 he received the M.D. degree at the University of Kansas. At the University of Kansas Medical School at that time, such outstanding men as Dr. Ralph Major, Dr. Peter T. Bohman, Dr. John Sundwall and Dr. Richard Sutton were among the faculty. Dr. Sundwall later came to the University of Minnesota as the first Director of the Students' Health Service, with which Dr. McKinlay was associated.

Internship at the Montreal General Hospital in 1916 and 1917 was under the masterful physician and internist, Dr. Alvah H. Gordon. Dr. Gordon had been an associate at the Montreal General Hospital of Dr. William Osler and, in Dr. McKinlay's recollection, had everything that a great teacher should have. During the period of his internship, typhoid fever was common in Montreal and the disease, together with its complications, was considered almost an epitome of medicine.

In 1918 Dr. McKinlay was commissioned a lieutenant in the Medical Corps of the United States Army and ordered to Yale Army Laboratory School for active duty. While there he recovered from pneumococcus type I lobar pneumonia after the now obsolete treatment with unrefined type I antipneumococcus serum, which was obtained from Dr. Coles' Laboratory at the Rockefeller Institute in New York.

Dr. McKinlay came to Minnesota in 1919 as a medical resident in the University Hospitals under Dr. Leonard G. Rowntree. While still a

RUTH E. BOYNTON is retired as director, Students' Health Service, University of Minnesota.

medical resident he became a part-time consultant in internal medicine at the Students' Health Service in the year 1920, when Dr. John Sundwall was still the Director of the Health Service. Dr. McKinlay continued to serve as medical consultant to the Health Service until 1959.

Upon completion of his medical residency, Dr. McKinlay started private practice in internal medicine in the City of Minneapolis and is continuing his work in that field. Although his private practice has been an extremely busy one, he has always been one of the most conscientious and generous consultants that the Health Service has ever had.

In 1921 Dr. McKinlay married Kathryn Thorbus, who was graduated from the University that year with a B.A. degree and a major in sociology. Their first-born son, Donald, died in childhood. Gordon, the second son, is now associated with his father in the practice of internal medicine in Minneapolis. The third son, Robert, is a Y.M.C.A. secretary in Seattle, Washington. The McKinlays have one daughter, Eleanor, who is the youngest child. Dr. and Mrs. McKinlay now have six grandchildren who keep them young. Besides being a devoted homemaker, Mrs. McKinlay has been very active in church and civic affairs for which she has received well-deserved recognition by being included in *Who's Who of American Women*.

Dr. McKinlay has always been a staunch believer and supporter of the private practice of medicine, the free choice of physician, and the private enterprise system. He has been active in local and state medical organizations and has been, since its inception, one of the designers and officers of the Blue Shield Medical Plan in Minnesota. He has given unstintingly of his time to these organizations and it is impossible to assess the value of his contributions to them.

Next to the great satisfactions in the practice of internal medicine, Dr. McKinlay has always been a believer and teacher of the value of preventive medicine. As a member of the consulting staff of the Health Service his contributions to

the field of preventive medicine for university students have always been great. As a consulting member of the Health Service staff, he recognized the opportunities for teaching University students the preventive aspects of health care.

In his many years in private practice and as consultant to the Health Service, Dr. McKinlay has published many significant papers. In collaboration with Dr. J. A. Myers, he was one of the editors of a 2-volume series on *Diseases of the Chest and Heart*. One of Dr. McKinlay's early papers was on infectious mononucleosis, which he published with Dr. Hal Downey in 1923. Up to that time the hematology and clinical picture of infectious mononucleosis was little understood or studied. Infectious mononucleosis has now become a universal disease with an astounding number of articles in the literature. However, Dr. Downey's blood plate, as described in the original article, remains today for the expert hematologist the most precise diagnostic procedure for recognition of infectious mononucleosis. Similarly, Dr. McKinlay's clinical description has had few additions since that time.

Dr. McKinlay has also had numerous publications in various aspects of cardiology, a field which has been of particular interest to him throughout his professional career. Because he believes that unusual clinical experiences should be reported, he has contributed articles on several other aspects of internal medicine and has encouraged younger doctors to do likewise.

In the 40 years in which it has been my privilege to be associated with Dr. McKinlay, I have been impressed with his integrity, honesty, generosity in encouraging and helping his younger colleagues, and his complete devotion to any task he undertakes. We in the Health Service have missed his wise counsel, since University regulations no longer permit him to continue on the University staff. As a staff we are grateful for having had the opportunity to know and work with him.

Book Reviews . . .

Diagnostic Tests in Infants and Children

HANS BEHRENDT, M.D., *second edition, 1962. Philadelphia: Lea & Febiger. 617 pages. Illustrated. \$15.00.*

This book is exceedingly valuable to doctors who are in the fields of pediatrics or pathology or in general practice. I find that the author's discussions of general metabolism and various basal metabolic problems, carbohydrate metabolism tests, fat metabolism, and protein metabolism (the latter being divided into the various serum protein fractionations), and blood amino acids are complete and easily understood. Electrolyte metabolism, about which all of us are so conscious nowadays, together with utilization of calcium, phosphorus, sodium, potassium, and chlorides, is well discussed and has an excellent reference system. A doctor should be able, through using this book, to order laboratory procedures that will help him in his diagnosis. Tests of acid-base balance, hydration, acidosis, and alkalosis are somewhat hard to understand, and yet it is difficult for an individual to write on this subject without going into detail. The use of graphs and figures seems to have accomplished this very well. I find that the chapter on vitamin nutrition tests is excellent and, at this stage in our medical practice, exceedingly important in that many times we find the parents of children giving excessive amounts of the various vitamins, thinking that they can do no harm.

The digestive function tests are described in detail, including the gastric secretion tests, intestinal absorption tests, pancreatic function tests, and liver function tests. The cardiovascular chapter has been simplified exceedingly well. It is easy to read and very understandable. Endocrine function tests are becoming more and more important in that we are seeing the various endocrine dysfunctions and hypofunctions, and it is necessary for most doctors to be able to diagnose many of these in their early stages or in their mild forms in order to see the proper development in children. The last chapter on selected hematologic tests is very clear. It is important to consider various tests which the author has described in diagnosing many congenital hematologic diseases.

I find that this book is informative, helpful, and a great aid in ordering laboratory procedures. It is presented in a short, but clear, form. The quality of his illustrations and the over-all appearance of the book certainly add to the value and encourage those who are interested in children to have it available in their medical practice.

EDWARD N. NELSON, M.D.
Minneapolis

Psychochemotherapy: The Physician's Manual

EDMUND REMMEN, M.D., SIDNEY COHEN, M.D., KEITH S. DITMAN, M.D., and JOHN T. FRANTZ, M.D., 1962. Los Angeles: Western Medical Publications. 152 pages. Illustrated. \$4.50.

Today, through drug therapy, there are more and more psychiatric problems being treated by general practitioners. With prolongation of life, the mental problems of the aged have come to the fore, and psychotropic

agents enable these people to function in the community. The field of psychopharmacology is constantly increasing and, with the advent of new basic compounds and variations of current drugs, it is necessary for the busy physician to understand the nature and use of these agents.

The authors have presented a concise classification of mental disease, a brief review of diagnostic aids, and a well-planned section on the currently known biochemical aspects of mental illness. The remainder of the book is devoted to the psychotropic drugs—their classification, action, indications, side effects, and contraindications. Some of the drugs have been described in great detail, including results of animal experimentation and clinical studies, while others are mentioned only briefly. The lengths to which various drugs have been described do not necessarily coincide with the usefulness of the drugs. The appendix provides a good survey of current pharmacologic agents, including dosages, emphasizing side effects, cautions, and contraindications. (It would have aided the reader further had the authors referred to their text in the appendix so that elaboration on specific drugs could be found readily.) With an understanding of the broad categories, it is possible to administer a different type of compound to a patient not responding to the initially prescribed drug; for example, monoamine oxidase inhibitors as opposed to antidepressants not possessing this property. Caution should be exercised when changing compounds or when using combined compounds, and the authors have mentioned the contraindications and precautions. These cannot be overemphasized and could have been elaborated on more fully.

This book provides an understanding of psychochemotherapy, which is so vital to the physician before prescribing these drugs. The material is well presented and should be of help to any physician dealing with mental problems.

PATRICIA SHARPLEY, M.D.,
Minneapolis

Current Gastroenterology

CORDON MCHARDY, M.D., *editor, 1962. New York: Paul B. Hoeber, Inc. 674 pages. Illustrated. \$16.50.*

This book will be a helpful addition to the office bookshelf of the practicing physician. It deals with gastrointestinal disease, largely from the standpoint of diagnosis and treatment. The 57 chapters represent the contributions of 74 authors who participated in an American College of Physicians Postgraduate Course in Gastroenterology. Five of these chapters are devoted to esophageal disease. The reader will find the chapter on the "Stimulating Effects of Various Foods on Gastric-Acid Secretion," by Dr. Code, of special value in planning rational ulcer management; the following chapter by Dr. Grossman on the "Physiologic Approach to Medical Management of Duodenal Ulcer" emphasizes some simple but extremely important points concerning the views of antacids and other agents in the treatment of duodenal ulcer. Many newer entities to gastroenterology are discussed. Fluorocinematography, use of the fibroscope, gastrointestinal abnormalities in collagen disease, adult fibrocystic disease, intestinal biopsy, and the effects

(Continued on page 16A)



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BOOK REVIEWS

(Continued from page 454)

of serotonin on the gastrointestinal tract—all subjects about which most of our knowledge has accumulated in the past ten years—are treated in a comprehensive fashion. The book is well indexed and attractively bound.

JAMES B. CAREY, JR., M.D.
Minneapolis

Pediatrics

L. EMMETT HOLT, JR., RUSTIN MCINTOSH, and HENRY L. BARNETT, 13th edition, 1962. New York City: Appleton-Century-Crofts. 1,395 pages. Illustrated. \$18.00.

The thirteenth edition of Holt, McIntosh and Barnett's *Pediatrics* is the first revision since 1953. The format of this edition varies considerably from that of the twelfth edition; the latter has full page single column subjects, whereas this edition is double-columned and the print is somewhat smaller and lighter, making the pages somewhat easier to read than the previous edition.

This book has some 90 less pages than the twelfth edition and has been concentrated to that extent with apparently very little loss of actual valuable material. A noticeable change in this edition is that the growth charts, which in the former volume are located on the inside covers of the book, are now placed in the appendix. This does not make them quite as available as they were previously but does add somewhat to the appearance of the book.

The subject of pediatrics is covered rather thoroughly with the possible exception of the surgery and orthopedics of childhood. These, of course, could not be covered in a book this size because it would make a single volume too large. There are entire books on pediatric surgery and orthopedics.

Upon perusing the different chapters throughout the book, there are several that I feel deserve particular mention. The roentgenograms and the reproductions in the chapters on the chest and circulatory system are excellent and well worth study by the pediatrician. There is also a chapter of psychophysiologic problems which is very good. The nervous system is covered thoroughly and is especially interesting.

Another chapter deals with enteroviruses. This is a new section and one which should be read by every practitioner, since this subject is comparatively new. The chapter on infectious diseases is also well written and contains all the material essential to the diagnosis and treatment of these common diseases of children.

One feature of this book is a 2-page inclusion in the appendix of "Instructions for parents of diabetic children." This is of particular interest to those interested in treating diabetes in the younger age group.

A chapter on diseases of the throat and, particularly, indications for and against adenotonsillectomy, is excellent. This field, of course, is still debatable among pediatricians everywhere, and there is considerable meat for thought in what is written about this problem.

The subject of mesenteric adenitis is also included and is now considered an entity. This condition, because of its close similarity to acute appendicitis in childhood, is of particular value. It is interesting to note that it is described in detail, inasmuch as practically all surgeons doing childhood surgery have at times operated upon a supposed acute appendix only to find enlarged mesenteric nodes throughout the lower abdomen.

This book, which is the outcome of an original vol-

ume of "Diseases of Infancy and Childhood" written in 1896 by L. Emmett Holt, has passed through many editions and is now edited by his son L. Emmett Holt, Jr., and Drs. Rustin McIntosh and Henry L. Barnett. Upon reviewing this book and comparing it to Nelson's *Pediatrics*, the comparison in my mind is similar to that of Gray's and Cunningham's *Anatomy*. Both are excellent publications. Holt's *Pediatrics* is written by 81 pediatricians who are mostly professors or assistant professors of pediatrics in the medical colleges of the United States. These men are authorities in their own field and so have written in each case good treatises upon the subjects assigned to them. It is my feeling that either Nelson's or this volume could be used by the student of medicine or the pediatrician and should be owned by them as well as the general practitioner. The volumes are so similar in content, size, and format that there is little to choose between the 2 so far as I am concerned.

Anyone doing pediatrics should possess one volume or the other and refer to it frequently in his practice.

R. D. NIERLING, M.D.
Jamestown, North Dakota

The Human Testis: A Clinical Treatise

LEONARD P. WERSHUB, M.D., 1962. Springfield, Illinois: Charles C Thomas. 250 pages. Illustrated. \$10.50.

The 14 chapters cover, respectively, the differentiation of the gonads, the influence of hormones thereon, the histology of testicular development, the 17-ketosteroids, chromosomes and chromatin sex, sex determination, spermatogenesis, cryptorchidism, hypogonadism, the testes and adrenals, testicular neoplasms, transvestism, and the aged testis. Lesions of the testis other than those mentioned above are not discussed, and it seems to the reviewer that a better title would have been "The Endocrinology of the Human Testis." The subjects discussed are well covered, and the book should be of considerable interest to urologists both in training and in practice, to internists, to general practitioners, and to medical students. It is loaded with useful information and its bibliography affords ample access to the literature.

Unfortunately, the author's bland disregard of some of the more elementary rules of grammar (plural subjects with singular verbs and vice versa), his often needlessly involved sentences, and the innumerable misspellings both of proper names and of common terms and abbreviations make this otherwise excellent book very difficult to read with satisfaction. Your reviewer doubts that the publisher had the manuscript edited or that anyone could have read the author's proofs. Both author and editor deserve sharp raps upon the knuckles with a stout wooden ruler for these offenses.

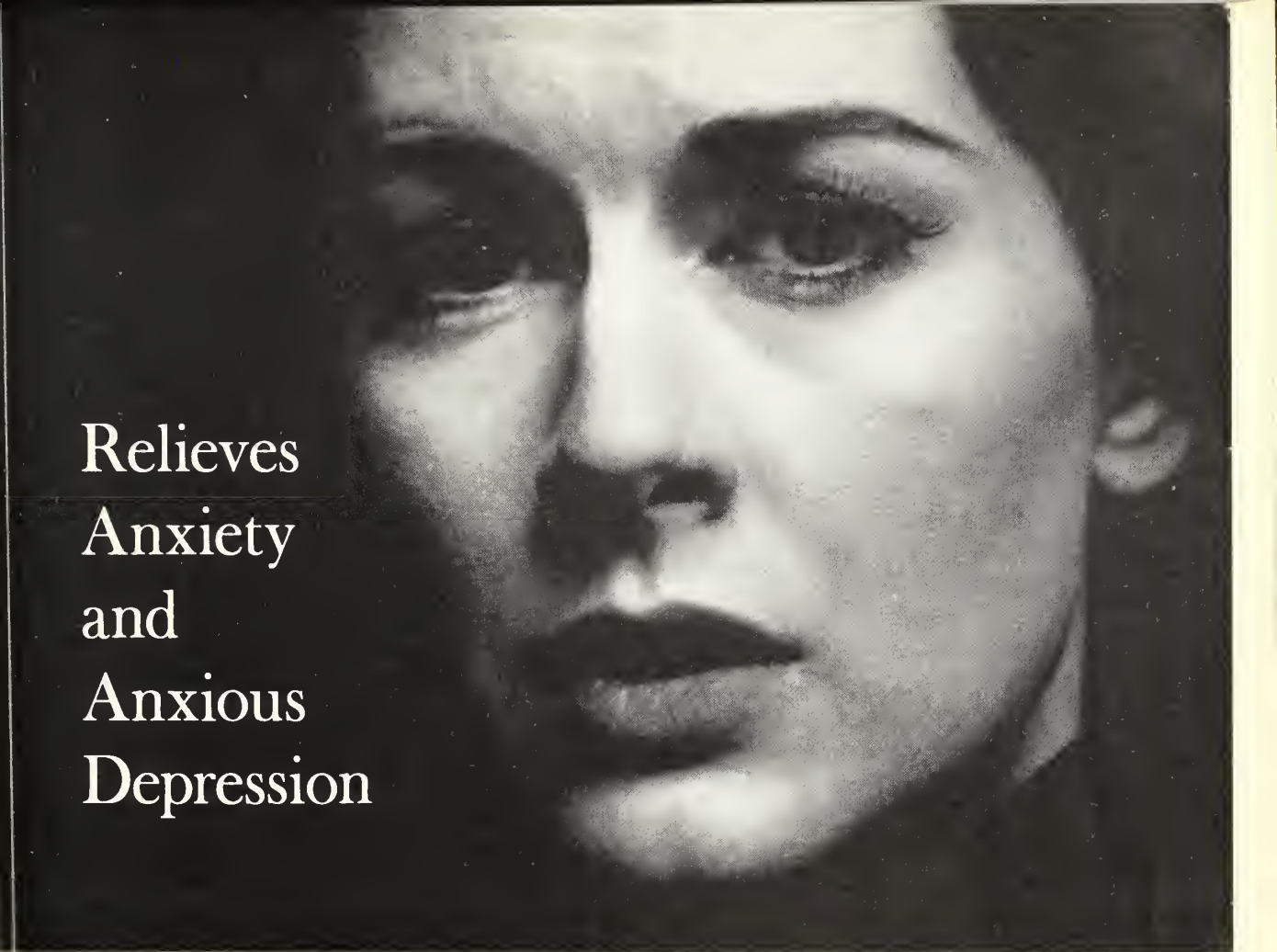
C. D. CREEVY, M.D.
Minneapolis

Postpartum Psychiatric Problems

JAMES ALEXANDER HAMILTON, M.D., 1962. St. Louis, Missouri: The C. V. Mosby Company. 156 pages. \$6.85.

This book is 147 pages in length and deals with the broad range of psychiatric problems which disturb a few women after parturition. The author presents his concepts of the problems and his methods of therapy. His

(Continued on page 18A)



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BOOK REVIEWS

(Continued from page 16A)

views are derived empirically, and he turns to literature for support. The value of the book lies chiefly in the fact that it calls attention to the possibility of postpartum psychoses and affords a historical review of some of the attitudes toward them. The author's views are largely physiologically oriented. He gives considerable attention to the use of thyroid and triiodothyronine in the treatment of these illnesses, particularly in the depressive stage. These views are only at the level of a "hunch" and are not documented in such a way that the responses he describes can be evaluated on the basis of controls. The author fails to define the length of the postpartum period, except that one gathers it means sometime after the birth of a child. The descriptions of thyroid deficiency do not fall outside the normal ranges for the test described. Considerable attention is given to his idea that postpartum psychoses are different from other forms of mental illness in respect to etiology, prognosis, and therapy.

This is at variance with the predominant view. His use of the term "dissociative syndromes" as synonymous with "the group of schizophrenia" is unfortunate and fails to conform with the definitions of the American Psychiatric Association.

Hamilton's recommendations for treatment are open to question. He fails to describe the use of the several major tranquilizers and antidepressants for which beneficial effects have been established.

The extensive review of the literature should be of value to other investigators interested in this area. However, the book is unlikely to become popular with general physicians, psychiatrists, obstetricians, or endocrinologists.

TITUS P. BELLVILLE, M.D.
Minneapolis

The Senile Brain: A Clinical Study

R. S. ALLISON, M.D., 1962. Baltimore: Williams & Wilkins Co. 288 pages. Illustrated. \$10.00.

The results of twenty years of clinical study involving cases of brain disease which present with mental deterioration are covered in this volume. The author, who is consulting neurologist to the Royal Victoria Hospital, Belfast, has made a special study of the subject, and every page of this well-written and valuable book bears witness to the critical precision of his work.

Many will quarrel with his choice of title. Among the 198 cases on which the book is based, no less than 57 were under the age of 50. The author does not confine himself to a study of the brain in old age, as his title suggests; rather, this is a study of cases of brain disease among persons of all ages in whom the presenting physical sign was dementia. This is a minor criticism of a book otherwise commendable, but it deserves mention. In fact, among the 198 cases studied, there are none listed as cases of senile dementia. Does this imply that the author does not recognize the occurrence of cases of cortical atrophy in old age where no cause other than senility is found? Some comment on this aspect would have been welcome.

The book is well arranged. There are excellent introductory chapters on history taking and the general and neurologic examination, with special reference to difficulties in examination peculiar to these cases. Following this, the acute and chronic disturbances of consciousness are examined and then disorders of speech and lan-

BOOK REVIEWS

guage. The section on parietal lobe syndromes is particularly good and thorough. On the other hand, some readers will wish that the chapter on ancillary methods of diagnosis, which gives the roentgenographic, lumbar puncture, electroencephalographic, and air study findings, had been expanded. There is room here for tables of results, specimens of tracings, and more illustrations. This section, though too brief, contains some startling findings. It was a surprise to the reviewer that an abnormally high spinal fluid protein was commoner in cases of cortical atrophy than in cases of tumor. This is certainly not the common belief and deserves special comment. The author wisely devotes a section to the affective disorders and stresses the frequency with which depressive illness may be confused with organic syndromes. He concludes with a chapter full of good sense about the treatment and management of dementia.

This is a book which I cannot recommend too highly to neurologists, psychiatrists, psychologists, and geriatricians. Internists and general practitioners will also find the book invaluable; and for myself, I should be happy to know that each of my medical students had had it out of the library for a day or two.

Probably its greatest value is to emphasize that underlying the physical sign, dementia, is a wide range of causes and that this sign demands thorough inpatient investigation in all cases. One wonders how many patients with undiagnosed operable cerebral tumor have died under the label "arteriosclerosis."

The author should be congratulated on a first-rate book in the best tradition of British neurology. It deserves a very wide sale, indeed.

LEONARD D. OSLER, M.D.
Boston

Transplantation of Tissues and Cells

R. E. BILLINGHAM and WILLYS K. SILVERS, editors,
1961. Philadelphia: The Wistar Institute Press. 149
pages. Illustrated. \$7.50.

Although chimera, the monster with a lion's head, a goat's body, and a serpent's tail, is still a creature of imagination, the authors of this book point out that an important experimental approach to gerontology requires the production of "age chimeras." In this sense, chimera refers to the mixture of tissues of different genetic constitution in the same part of an organism, a technique valuable "so that transplanted tissue and organs can be maintained in a normal and functionally reactive state for periods greatly exceeding their normal life expectancy." Grafts are also used for experimental approaches to immunology, cancer biology, endocrinology, and many other fields. Because of this significance, a group of noted biologists have contributed to the practical, clearly written, and well-illustrated book under review. Edited by 2 experienced scientists, this volume will prove to be useful in the laboratory of investigators in various disciplines involving the transplantation of cells and tissues.

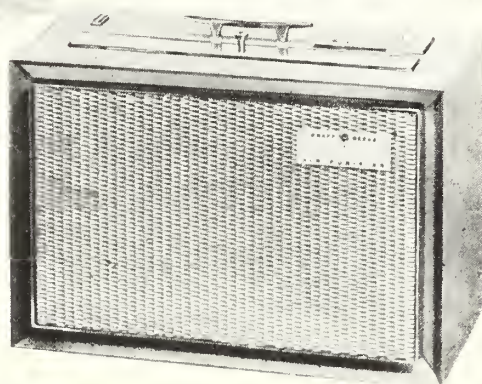
Contents include, among others, discussions of skin grafting in mammals, in newborn rats and mice, and in birds; endocrine grafting techniques; comments on parabiosis; and even a definition of inbred strains and advice on their maintenance.

The practicing physician or surgeon should not search in this book for procedures immediately applicable to man; such techniques are beyond the scope of this valuable vademecum for the research worker.

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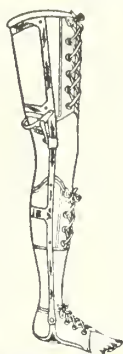
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News Briefs . . .

General

DR. RICHARD E. PAYNE, Virginia pediatrician, has returned from volunteer service in Garona-Boulai, Cameroun, west central Africa. He discovered that customs of a mission station hospital, compared with those of the East Range Clinic in Virginia, were somewhat unusual. Friends and relatives of patients would fill the hospital units with smoke as they cooked their meals and visited at the same time.

North Dakota

DR. HOWARD R. GRAY, a native of Mississippi, has joined the Quain and Ramstad Clinic in Bismarek where he is organizing a department of dermatology. Dr. Gray is a graduate of Washington University School of Medicine, St. Louis.

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DR. ALEX THIERY has been appointed temporary clinical director of the outpatient treatment program at North Dakota State Mental Hospital, Jamestown. He replaces Dr. Sushenkumar Thakor, who recently resigned from the post.

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DR. LEONARD E. WOYTASSEK, Michigan, North Dakota, physician, has moved to Omaha to join the Nebraska Neuro-Psychiatric Institute.

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DRS. HUGH H. JOHNSTON and Gerald Sailer have been assigned to the staff of the Public Health Service Indian Hospital in Belcourt. Dr. Johnston is from Vicksburg, Mississippi, and received his medical degree from Vanderbilt University School of Medicine, Nashville. Dr. Sailer, who is from North Dakota, is a graduate of Baylor University College of Medicine, Houston, and interned at St. Luke's Hospital, Duluth, Minnesota.

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DR. MYRON D. PETERSON, a native of Norwich, has become a member of the staff of the Medical Arts Clinic at Minot. Dr. Peterson received his medical degree from Northwestern University Medical School, Chicago.

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DRS. JOSEPH W. MILLER and James B. Wenzel have joined, respectively, the departments of orthopedies and pediatrics at the Dakota Clinic in Fargo.

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DR. R. NATARAJAN, recently a member of the staff at the Yankton State Hospital, South Dakota, has joined Dr. H. Angus Bowes at Grand Forks. A native of India, Dr. Natarajan is a specialist in psychiatry and neurology. He graduated in 1939 from Stanley Medical College, Madras, India.

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DRS. DONALD A. SWETTER and Fred Schaldach have been assigned to the Public Health Service Indian Hospital at Fort Yates. Dr. Swetter is from Forest City, Pennsylvania, and Dr. Schaldach from Madison, Wisconsin.

Surgery for Pulmonary Tuberculosis Analysis of Long-Term Results

RICHARD W. ERNST, M.D., and

LYNN CHRISTIANSON, M.D.

Dallas and New York City

A REVIEW of the recent literature on the treatment of pulmonary tuberculosis reveals that there is significant success obtained with the newer drugs if these are used intelligently.¹⁻⁴ As a result, fewer patients will require surgical therapy.^{4,5} This is also due in part to the fact that in more civilized communities the tuberculous patient tends to seek medical help earlier. At the present time, in general, surgery is advised mostly in far-advanced or medical failure cases.⁶

Our purpose is to present surgical results with long-term follow-up of an admittedly small, but nevertheless totally unselected, number of patients primarily belonging to the lower income group.

MATERIAL AND METHOD

A total of 78 surgical procedures were performed on 60 patients. There were 53 pulmonary resections consisting of 23 lobectomies, 3 pneumonectomies, and 27 segmental resections. The rest constituted collapse therapies in the form of thoracoplasties, methyl methacrylate ball, and Ivalon sponge plombages.

Pulmonary function studies consisting of total

and half-second timed vital capacity in the immediate preoperative period and one to three months postoperatively are reported. All patients had preoperative and postoperative sputum examination. Surgical specimens from 26 were obtained for culture. The results are presented and compared with the preoperative sputum cultures. Finally, a report is given on the patient's condition from four to five years following surgery.

RESULTS

There were 2 deaths in the group. Neither subject would be a surgical candidate with our present knowledge. The first patient had had a 3-stage thoracoplasty on the right side in 1947. He had far-advanced active disease on the left. Collapse therapy was recommended for the left side, and an Ivalon sponge plombage was done. The patient died on the operating table of acute respiratory insufficiency. Obviously, we should not have recommended surgery in this patient since he had virtually no pulmonary reserve. The second death was that of a patient with far-advanced emphysema. His total vital capacity was 58 per cent of that predicted, and his first half-second expired air was 18 per cent of the total. This patient had a resection of the left upper lobe and superior segment of the left lower lobe. A tracheostomy was done at the

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TABLE 1
MAJOR COMPLICATIONS

Type	Cases, no.
Persistent bronchopleural fistula with or without empyema requiring drainage from one month to one year	1
Subscapular space infection	2
Bronchopleurocutaneous fistula requiring thoracoplasty	2
Persistent pain requiring revision of thoracoplasty	1
Persistent sterile extrapleural fluid collection in a case of methyl methacrylate ball plombage relieved when lucite balls were removed	1
Total	7

TABLE 2
MINOR COMPLICATIONS

Type	Cases, no.
Small apical air pocket undergoing spontaneous resolution	4
Continued air leak from four days to one month	4
Small wound infection cleared in three weeks	2
Chest wall hematoma due to poor hemostasis	1
Total	11

time of surgery to assist respiration. However, the patient developed acute cor pulmonale and died eight hours after surgery.

There were 18 surgical complications (30 per cent), of which 7 were major and 11 minor. These are listed in tables 1 and 2.

Preoperative and postoperative total vital capacity and also vital capacity for one-half second timed intervals were averaged for all cases. This is summarized in table 3.

All but 2 patients had had drug therapy from four months to four years before surgery. Duration of therapy was less than six weeks in 2 cases; bronchogenic carcinoma was suspected in addition to tuberculosis in both of these patients, and early surgery was advised. Sputum was positive in 18 patients before surgery. One of these patients had received tuberculosis therapy for only two weeks before operation. The 2 persons who died in our series had had positive sputum. The remaining 16 patients have had a follow-up of four to five years with the exception of one who was lost to follow-up two years after operation. He had negative sputum immediately after surgery and thereafter until he was lost to follow-up, however. Only 2 of these 16 patients

still have positive sputum; 1 patient had a thoracoplasty and continued with positive sputum, and cavitory tuberculosis developed in the opposite lung immediately after resectional surgery in the other. The latter patient was totally resistant to all drugs before surgery and remained so following operation.

Cultures of the surgical specimen were obtained in 26 cases. Of these, 7 had positive and 19 had negative sputum preoperatively. It is interesting, however, that 21 surgical specimens grew positive cultures. The cultures were positive in all 7 patients with positive sputum but, in addition, 14 patients with negative sputum before surgery had positive tissue cultures. The tissue pathology revealed that 13 patients had caseation with cavitation, 9 had caseation alone, and 4 had cavitation alone. In addition, 10 of these 26 patients had endobronchitis or broncholithiasis or both in the resected specimen.

Sensitivity data from sputum and tissue culture from the same patient are available in only 5 instances. It is of interest to note, however, that in only 1 of these 5 patients did we obtain the same sensitivity from the sputum and the tissue cultures. In the remaining 4 there was a marked difference between the sensitivities of the 2 cultures.

The two-year follow-up includes 57 of the 58 survivors. Of these, 2 patients—the same 2 mentioned previously—continued to have positive sputum. The remainder of these patients were up and well with the exception of 1 who has been suffering from advancing emphysema which was present before surgery. Of the 58 patients, 51 were followed for four years or more. Records show negative sputum at the time of discharge for all 7 patients lost to follow-up. Of these 51 patients we found again that 2 continued with positive sputum. The remainder were free of disease. This left us with a 3.8 per cent continuation of positive sputum following surgery.

DISCUSSION

In the analysis of the results on the cases pre-

TABLE 3
PULMONARY FUNCTION TEST

Total vital capacity and one-half second timed vital capacity	
Preoperative (average)	Postoperative (average)
Total vital capacity 69 per cent of predicted vital capacity	Total vital capacity 67 per cent of predicted vital capacity
One-half second timed vital capacity 59 per cent of total vital capacity	One-half second timed vital capacity 61 per cent of total vital capacity

sented it becomes evident that surgery should not be excluded from the therapeutic armamentarium for pulmonary tuberculosis. The 3.8 per cent failure of conversion does not represent relapse but rather a continuation of disease in spite of medical and surgical therapy.

All other cases available for follow-up are free of active tuberculosis four and five years after operation. This compares very favorably with reports in the literature where patients who had medical management alone demonstrate a relapse from 3 to 10 per cent in a long-term follow-up.^{7,8} Our complication rate compares favorably with that reported in the literature.⁹⁻¹¹ All of our complications cleared in the normal time the patient would spend in a sanatorium or at home during antituberculosis therapy. As a result, none of these complications prolonged the patient's convalescence.

The internist who assumes full responsibility for the treatment of pulmonary tuberculosis without considering surgery will have to be a very thorough and conscientious doctor. The initial therapy and very close and thorough follow-up are the only weapons he has to avoid a possible relapse or early drug resistance.^{1,3-5,12,13} Our series demonstrates with others¹⁴ that it is a definite mistake to consider pulmonary tuberculosis a purely medical disease. Surgery still has a very definite place in the treatment of tuberculosis. It is true that the very aggressive early resection should not be employed any more unless one strongly suspects a neoplasm. Resectional surgery should be considered in the following conditions:¹⁵ (1) Round lesions of undetermined etiology; (2) symptomatic tuberculous bronchiectatic lesions; (3) excretion of drug resistant organisms before conversion; (4) sudden bacteriologic remission not attributable to chemotherapy; and (5) ethnic predisposition of progressive tuberculosis and sociologic factors precluding adequate therapy or follow-up study. One can add to these indications the following:⁷ Destroyed lung, large cavities, large nodules, and bronchial stenosis. Finally, patients who have a scarred fibrotic lung following active tuberculosis with evidence of a nodule in this area may develop a neoplasm. Whether a scar in the lung predisposes to bronchogenic carcinoma or not is difficult to determine. However, more and more reports appear in the literature^{7,16} indicating that this is a likely possibility.

Collapse therapy as the only surgical mode of therapy has just about fallen to the wayside. At the present time we occasionally employ tailored thoracoplasties in cases with a significant space problem.

SUMMARY

The procedures and the complications of 60 patients undergoing 78 surgical procedures are presented and preoperative and postoperative pulmonary function studies are tabulated.

In 26 cases the surgical specimen was cultured; results are compared with the patient's sputum culture. The pathologic tissue report is included in an effort to correlate positive or negative cultures, or both, with the respective pulmonary lesions.

An analysis of present-day surgical indications is presented, including the views of various other authors.

The two-, four-, and five-year follow-up results are presented with a recommendation that surgery should not be altogether forgotten, inasmuch as the presented cases compare favorably with results of medically treated patients presented in the literature.

This report represents work done at Parkland Memorial Hospital and Woodlawn Hospital, affiliated with Southwestern Medical School, Dallas.

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Spinal Fluid Pleocytosis in Systemic Lupus Erythematosus

A Case Report and Review of the Literature

ROBERT PIERCE, M.D., and JOHN LOGOTHETIS, M.D.

Minneapolis

NERVOUS system manifestations in systemic lupus erythematosus have been known almost since the disease was first described,¹ but only since Hargraves described the LE cell in 1948 has the full extent of such complications been appreciated. In 44 of their own cases and in an additional 279 collected from the literature, Jessar and associates² reported 5 per cent toxic psychoses, 9 per cent convulsions, and 2 per cent hemiplegias as the major manifestations. We do not intend to review the nervous system signs and symptoms of this disease, since this has been done previously.³⁻⁷ The importance of meningeal involvement in this disease became apparent to us after we saw a case with psychiatric and neurologic findings in which a significant spinal fluid pleocytosis and elevated protein were present. Since such spinal fluid findings associated with systemic lupus erythematosus are rare, it was felt that the case should be presented and discussed in detail.

CASE REPORT

A 41-year-old housewife was first admitted to Minneapolis General Hospital in March 1958, complaining of pleuritic chest pain, fever, loss of weight, and nonproductive cough for the previous three weeks. She gave a history of frequent pleuritic chest pain for the past three to four years. Her husband thought she had been acting strangely for the past few years, mainly because of her thoughts of persecution and accusations about him and their children. She had mentioned suicide and had threatened to shoot her husband.

On examination, her temperature was 103° F.; pulse was 90; and blood pressure was 94/50. She appeared chronically ill. Her skin was free of lesions. The ocular vessels were unusually tortuous. No lymph nodes were enlarged. There was evidence of consolidation at the base of the left lung. The heart was normal. The liver and spleen were not felt. The extremities presented nothing abnormal except for some muscle atrophy in the left leg, resulting from an old poliomyelitis. The

neurologic examination was normal. The laboratory findings included hemoglobin of 10.6 gm. per cent and urinalysis with a trace of albumin and an occasional pus cell. The white blood cell count was 12,400 per cubic millimeter with 87 per cent segmented forms. Erythrocyte sedimentation rate was 102 mm. per hour. Blood urea nitrogen, blood sugar, and serum proteins were normal. Sputum and blood cultures grew pneumococci. Mantoux skin test was negative. Because of a positive serologic test for venereal disease, a positive Wasserman, and a negative history of lues, a lupus cell preparation was done. It revealed leukocytes with inclusion bodies, but not typical of lupus cells. The cerebrospinal fluid was clear, with normal protein and cell content and negative Wasserman reaction. Colloidal gold curve was 11111-00000. She was afebrile in twenty-four hours after receiving penicillin and was discharged on the tenth day with the diagnosis of pneumococcal pneumonia.

Her second admission was in August 1958 for almost the same complaints as the first admission. Her temperature on admission was 100.6° F. The chest showed consolidation. A pleural friction rub was present over the right lung base. Axillary and inguinal lymph nodes were slightly enlarged. The electrocardiogram was compatible with pericarditis. Hemoglobin was 9.9 gm. per cent, and white blood cell count was 10,300 per cubic millimeter with 82 per cent segmented forms. The urinalysis showed only an occasional pus cell. Erythrocyte sedimentation rate was 91 mm. per hour. A sputum culture grew alpha streptococci and pneumococci. Sputum samples were negative for acid fast bacilli. Antistreptolysin titer was 500 Todd units. Cold agglutinins were positive in dilution of 1:128. Serum complement fixation was negative for psittacosis. Thymol turbidity was 13 units. Cephalin cholesterol flocculation was 2 plus. Kidney excretion tests were normal. There were no lupus cells seen in 3 preparations. She ran an intermittent temperature to 101° F. for two weeks. Psychiatric consultation revealed a character disorder and no overt psychosis.

The third admission was only one week after her previous discharge. She was admitted to the psychiatric ward after threatening her husband and children. The patient was oriented but very hostile and paranoid. She was afebrile and complained only of occasional joint pains. She was treated for two weeks with ataractics and discharged to a state mental hospital. The patient received electroshock therapy during her four-month stay.

The fourth admission was in August 1960. For the previous year she complained of progressive weakness,

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headaches, fever, malaise, and joint pains, at times associated with swelling and increased warmth. On examination, her vital signs were normal. There were fine rales in both lung bases. The joints were painful to manipulation, especially the interphalangeal joints. Hemoglobin and white blood cell count were normal. Erythrocyte sedimentation rate was 70 mm. per hour. Urinalysis showed only occasional white cells. Phenolsulfonphthalein excretion was 13 per cent in one hour. Thymol turbidity was 10.5 units and serum proteins were normal. Agglutinations for *Salmonella typhi*, paratyphi B, and *Brucella* were negative. Lupus cell preparations were positive on 4 occasions and negative twice. Serum serologic test for venereal disease and Wasserman tests were both positive. A spinal tap performed the day after admission showed 104 cells, 34 per cent segmented forms and 66 per cent mononuclears, and protein of 160 mg. per cent. Spinal fluid Wassermann was negative and gold curve was 1111222111. The sugar was 44 mg. per cent, and the pressure was not measured but was thought normal. The spinal tap was repeated the next day with essentially the same results except that the cell count was then 44 with the same differential. Bacterial culture and stain of the fluid were negative. Three Mantoux skin tests were negative. A stained smear for cryptococcal organisms was negative. Smear for acid fast organisms was negative with culture and guinea pig inoculations subsequently proving negative. Blastomycin, coccidioidin, histoplasmin skin tests, and fungus culture were negative. A stool specimen produced no growth of viruses. A diagnosis of systemic lupus erythematosus with meningeal involvement was made and the patient was started on 60 mg. prednisone daily and 400 mg. hydroxychloroquine sulfate (Plaquenil) daily. She reported marked improvement in her headaches and weakness over the ensuing two or three days. She noticed also that her skin was no longer painful to the touch. The prednisone dosage was gradually lowered thereafter. A spinal tap performed two weeks later showed 42 cells, 21 per cent segmented forms, protein of 76 mg. per cent, and sugar of 65 mg. per cent. The erythrocyte sedimentation rate at this time was 8 mm. per hour. A third spinal tap one month after the initiation of therapy showed 32 cells, 35 per cent segmented forms, protein of 66 mg. per cent and sugar of 67 mg. per cent. She was discharged symptom-free at this time on 10 mg. prednisone and 400 mg. Plaquenil daily.

At her first clinic visit two months after discharge, she complained of some tingling of the left side of her face. The frontal headaches had also returned, but were less severe. A spinal tap was then repeated, and it showed normal pressure, a total of 7 mononuclear cells, 40 mg. per cent sugar, and 36 mg. per cent protein. The prednisone was then stopped, but the Plaquenil was continued. When last seen, three months after her discharge, the parasthesias and headaches had cleared but some weakness was present, and a dose of 2 mg. methylprednisolone (Medrol) daily was instituted.

DISCUSSION

The patient in this report is a rare example of chronic headaches with significant pleocytosis in the spinal fluid, occurring in the course of systemic lupus erythematosus. The neurologic picture responded promptly to prednisone and hydroxychloroquine. The same patient, at a pre-

vious exacerbation of the disease, developed a paranoid psychosis for which she had to be hospitalized for four months.

Reports of systemic lupus erythematosus with increased spinal fluid protein are common and are mostly associated with peripheral neuritis.⁸⁻⁹ Studies of real pleocytosis are scarce, however, and often omit data about microbial cultures and skin tests.^{6,10-12} The 6.4 per cent incidence of meningeal signs and pleocytosis in Dubois' 62 cases is uniquely higher than that reported in other studies.^{2,11} Although he mentions that the spinal fluid cell count may be as high as "several hundred leukocytes, either mononuclear or polymorphonuclear," specific values are mentioned in only 1 case in which the cell count was 128 cells per cubic millimeter, all lymphocytes. This was in a case of a 10-year-old boy who had a lumbar tap because of lethargy and positive serology. He responded well to steroids and was well after three months. On Harvey's 138 cases, 3 showed elevated spinal fluid cell counts ranging from 250 to 550 cells per cubic millimeter, although one of these was a case of cryptococcal meningitis.¹⁰ Of Sedgwick's 25 cases, only one diagnosed as toxic psychosis had a spinal fluid cell count of 18 cells per cubic millimeter.⁶ The diagnosis in this case was not a tissue diagnosis, and the LE cell test was not available at that time. It should not be surprising, however, to find meningeal signs and a number of cells in the spinal fluid as both Glaser¹³ and Malamud¹² in histopathologic studies report leptomeningeal necrosis and infiltration with mononuclear and polymorphonuclear leukocytes in the absence of complicating infection.

SUMMARY

A case of systemic lupus erythematosus with persisting headaches and a spinal fluid pleocytosis of 104 cells, 66 per cent of which were mononuclears, was presented. The same patient at a previous date exhibited signs of paranoid psychosis with normal spinal fluid findings.

Response to prednisone and hydroxychloroquine therapy was encouraging, with the patient's symptoms and spinal fluid returning to normal within two months after initiation of treatment.

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PATENT DUCTUS ARTERIOSUS usually should be immediately corrected surgically when definitive diagnosis is reached. Operation may be delayed a few months, however, for the asymptomatic infant with a normal growth rate and no roentgenographic or electrocardiographic abnormalities. Outcome does not seem to be affected by age, pregnancy, maternal rubella, previous rheumatic fever, or presence of noncardiac congenital anomalies. Results are poor in patients with reversal of flow through the ductus.

In the twenty-year period, 1938-58, patent ductus arteriosus was corrected in 435 patients. Most of the patients over a year old had a machinery-like murmur and a thrill which was greatest in the second and third left intercostal spaces. More than half of patients had only a systolic murmur during infancy. Because the findings were frequently indistinguishable from those of ventricular septal defect, cardiac catheterization and retrograde aortography were often necessary in infants to arrive at the correct diagnosis.

The ductus was tied off in 32 patients and divided in the rest. Ten surgical deaths occurred, all in patients who had had reversal of blood flow through the ductus. Three of the 10 deaths were in the last four years of the period.

L. JEROME KROVETZ and HERBERT E. WARDEN: Patent ductus arteriosus. *Dis. Chest* 42:46-57, 1962.

Use of a New Bronchodilator Combination, Bronkometer, for Acute Bronchial Asthma

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St. Paul

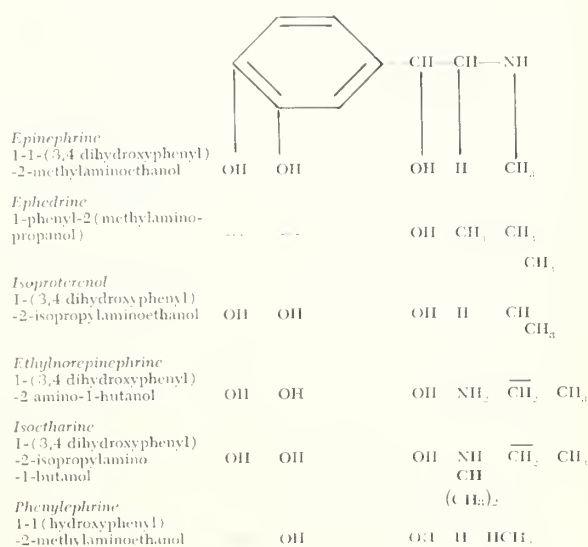
ALTHOUGH interest in asthma as a medical subject is old, aerosol therapy for control of the acute attack of bronchospasm is relatively new. The aerosol use of epinephrine hydrochloride was first proposed by Ephraim in 1910.¹ Interest in this technic lagged for the next twenty-five years because of the large volume of solution (1:1,000) necessary for relief of the severe attack. Nebulizers had not reached their present state of refinement. In 1935, Graeser and Rowe² worked with the 1:100 solution of epinephrine. Much smaller quantities were needed and interest in the inhalation route for therapy of bronchial asthma quickened. As advances in inhalation agents occurred, mechanical devices for their administration kept pace. Today, the physician has a choice of bronchodilator agents and a choice of devices for their administration.

Epinephrine provided the base from which molecular changes have been made. The figure gives the structural formula for commonly used sympathomimetic amines including the bronchodilator isoetharine (Dilabron), one of the active ingredients in Bronkometer, the subject of this report.

Various investigators have studied the mechanism of bronchoconstriction and have utilized animal and human experiments in the production and prevention of artificially induced bronchoconstriction. Histamine was first suspected to have bronchoconstrictive qualities in the early 1900s. Schenk³ demonstrated in 1921 that the respiratory distress produced by large doses of histamine was due to bronchoconstriction. Acetylcholine was studied at approximately this same time and, in 1937, Kallos and Pagel⁴ successfully produced experimental asthma with acetylcholine in the guinea pig. Moll,⁵ in 1940, reported that the subcutaneous administration of acetyl-beta-methylcholine in asthmatic subjects produced attacks "indistinguishable from spontaneous attacks of asthma." Various inves-

tigators since that time have used histamine or methacholine by injection, or aerosol, to study the relative strength of various therapeutic substances in preventing or controlling artificially induced bronchospasm. Vital capacity measurements or maximum breathing capacity measurements were determined at intervals to yield information on both the amplitude and duration of effect of the therapeutic agent under study.

Concurrent with the study of potency and duration of the various bronchodilators, measurements were made of the side effects produced. Epinephrine produces definite bronchodilation in therapeutic doses. However, central nervous system stimulation and effects on pulse and blood pressure may be disturbing. Subsequent bronchodilators have been developed which have the capacity to relieve bronchospasm without the strong tendency to produce side effects. The introduction of isoproterenol demonstrated the possibility of producing effective bronchodilation without serious central nervous system stimulation.



Structural formulae of
common sympathomimetic amines

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TABLE 1
COMPARATIVE PROTECTIVE VALUES OF ADRENERGIC AGENTS AGAINST HISTAMINE- AND METHACHOLINE-
INDUCED DYSPNEA AND BRONCHOCONSTRICTION IN ASTHMATIC PATIENTS

Protecting drug	Bronchoconstricting agent							
	Histamine, i.v.		Methacholine, i.v.		Histamine, aerosol		Methacholine, aerosol	
	Immediate protection (per cent)	Duration of significant (40%) protection, min.	Immediate protection (per cent)	Duration of significant (40%) protection, min.	Immediate protection (per cent)	Duration of significant (40%) protection, min.	Immediate protection (per cent)	Duration of significant (40%) protection, min.
Epinephrine 1:1000, 0.5 em. sc	100	143	90	83	70	127	40	72
Epinephrine 1:100, aerosol	75	28	56	18	89	36	66	17
Vaponefrin 2.25%, aerosol	93	27	74	18	90	53	87	40
Phenylephrine 1:100, 0.3 em. sc	13	0	13	0				
Phenylephrine 1:100, aerosol	52	16	32	0				
Isuprel 1:100, aerosol	98	62	91	81				
Isuprel 1:200, aerosol	70	22	69	42	84	21	65	25
Isuprel 1:5000, 0.5 cu. cm., sc	100	30	56	18				
Dilabron (Win 3046) 1:100 ce. aerosol	97	97	69	70				
Dilabron (Win 3046) 2.5% aerosol			86	64				

Ethylnorepinephrine (Bronkephrine), produces effective bronchodilation in therapeutic doses with minimal effect on the cardiac or central nervous systems. Its use has been restricted largely to intramuscular or slow intravenous injections.

Isoetharine is the newest introduction in the series of bronchodilator agents. This new adrenergic drug (1-[3,4-dihydroxyphenyl]-2-isopropylamine-1-butanol methanesulfonate) is a derivative of ethylnorepinephrine and isoproterenol. The isopropyl grouping of the latter drug is added on the nitrogen of the ethylnorepinephrine nucleus.

Herschfus, Rubitsky, and associates⁶ utilized trained asthmatic patients in an excellent study of the protection offered by various agents against the bronchoconstrictive effect of histamine or methylcholine used intravenously or by aerosol. A portion of the results of this study are reproduced in table 1.

Members of this same group⁷ reported their clinical experience with 1.75 and 2.5 per cent concentrations of isoetharine (Dilabron). Both of these solutions were administered from stand-

ard nebulizers and patients were instructed to take 6 inhalations to control an attack. Cardiovascular response was studied in detail in 5 of these patients who presented themselves to the laboratory with acute paroxysms of bronchial asthma. The authors state, "The average maximum alteration in blood pressure was a fall of 2 mm. in systolic pressure and 6 mm. in diastolic pressure. None of these cardiovascular responses were subjectively manifest." "In none of the patients did tachycardia, palpitation, or other side effects appear following the administration of six inhalations of this aerosol (2.5% and 1.75%)." (It should be noted the concentration of isoetharine is 0.6 per cent in the Bronkometer aerosol.)

Lands⁸ has studied all of the active ingredients in Bronkometer separately and in combinations. Table 2 outlines the protective effect of isoetharine and isoetharine combined with phenylephrine or phenyldiamine in the guinea pig exposed to a histamine mist.

Phenylephrine has been included in Bronkometer because of its mild but significant bronchodilator activity and bronchovasoconstrictor activ-

TABLE 2
PROTECTIVE EFFECT OF ISOETHARINE AND ISOETHARINE COMBINED WITH PHENYLEPHRINE OR THENYLDIAMINE IN THE GUINEA PIG EXPOSED TO A HISTAMINE MIST

Drug	Concentration (per cent)	Number of animals	Protection
Isoetharine	0.003	40	23
	0.010	46	57
	0.030	24	71
	0.100	26	92
Thenyldiamine	0.001	16	12
	0.003	26	27
	0.010	16	45
	0.030	16	81
Phenylephrine	0.250	10	0
Phenylephrine + isoetharine	0.100	20	5
	0.003		
Isoetharine + thenyldiamine	0.0015	20	20
	0.0015		
	0.0025	20	75
	0.0025		
	0.005	30	96
Isoetharine + thenyldiamine + phenylephrine	0.010		
	0.001	12	92
	0.0025		
	0.030		
	0.003	9	100
	0.0075		

ity. Dautrebande⁹ states, "The mixture of equal parts of Aleudrine-Neo-Synephrine furnishes a good example of synergistic action in the sense that the pneumodilation obtained by a half dose of each of these products in mixture is more notable than that furnished by the two products separately in double dose."

Miller¹⁰ has combined phenylephrine with bronchodilators and antibiotics for use in various respiratory diseases.

The addition of thenyldiamine to Bronkometer offers antihistaminic activity. Grant,¹¹ using the histamine challenge technic in guinea pigs, states, "The result obtained with the combination [isoetharine and thenyldiamine] has revealed a synergism."

MATERIALS AND METHODS

One hundred patients, 63 female and 37 male, were chosen from private practice in an effort to assess the efficacy of Bronkometer in the relief of acute paroxysms of bronchial asthma. Each of these patients, 18 to 79 years of age, had been diagnosed as having chronic bronchial asthma and had been under active treatment for at least one year, using one or more of the

nebulized bronchodilators for relief of the acute asthmatic attack.

The patients were instructed to continue their current prophylactic therapy utilizing Bronkotabs and desensitization. The use of steroids was restricted.

The patients were instructed to take 1 or 2 inhalations from the Bronkometer as soon as definite signs of an acute episode of bronchospasm appeared. Duration of therapy varied from one month to one year.

RESULTS

Clinical results of Bronkometer therapy in 100 chronic asthmatic patients are summarized in table 3.

A number of these patients were tested for timed vital capacity measurements during the course of treatment with Bronkometer. Intermittent positive pressure breathing therapy was given to members of this group to determine if additional improvement in vital capacity could be gained. Therapy was carried out with a similar formula containing isoetharine 1.0 per cent, phenylephrine 0.25 per cent, and thenyldiamine 0.1 per cent (Bronkospray). Dosage was 0.25 to 0.5 cc. in 2 cc. saline, nebulized in twenty minutes. Representative results of measurements and therapy are presented in table 4.

DISCUSSION

Results of therapy with Bronkometer inhalations in 100 chronic asthmatic patients have been encouraging. The use of this bronchodilator drug combination has been characterized by good relief of bronchospasm and almost total lack of systemic side effects. The patients who were tested for timed vital capacity measurements and those who received intermittent positive pressure breathing therapy were checked for pulse and blood pressure measurements. None of these patients exhibited significant changes in

TABLE 3
RESULTS

Results*	Number of patients	Per cent
Excellent	25	25
Good	64	64
Fair	8	8
Poor	3	3
Total	100	100

*Results were classified as excellent if relief of bronchospasm was clinically complete and lasted four or more hours, good if relief was complete and lasted two to four hours, fair if relief of bronchospasm was adequate but not total, and poor if relief was inadequate or of brief duration.

TABLE 4
COMPARATIVE INCREASE IN TOTAL VITAL CAPACITY
AFTER TWO INHALATIONS OF BRONKOMETER
AND IPPBM THERAPY WITH 6 DROPS OF BRONKOSPRAY

Patient	Total vital capacity		
	Pre-treatment	After 2 Bronkometer inhalations	After Bronkospray and IPPBM
M. T.	1800	2000	2300
D. C.	2100	2300	2900
M. C.	2400	2600	3400
M. L.	2300	2400	2700
S. M.	1700	2000	2600
E. N.	1300	1350	1500
V. A.	2400	2600	2800
M. A.	2000	2400	3000
J. A.	2400	2600	3000
L. D.	2000	2400	3200
L. F.	1800	2000	2600
P. M.	2600	2000	3700
A. L.	1800	1900	2200
C. S.	2000	2000	2200
R. T.	2600	2800	3500
J. C.	2400	2500	2800
R. C.	1600	1700	1700
A. S.	900	1200	1800
G. K.	1800	2100	2300

pulse or blood pressure. Bronkometer appears to be safe for use even in hypertensive patients. This lack of central nervous system and cardiac stimulation has been useful in promoting patient cooperation. Cooperation is particularly noteworthy during intermittent positive pressure breathing therapy.

Patients have been encouraged to cough after inhalation of the bronchodilator and report greater ease in expectoration of mucous plugs. Dilation of the bronchioles and reduction of congestion around the bronchioles promote easier passage of air. Elimination of mucous plugs and tenacious secretions helps to reduce the progression of changes in the respiratory system and increases vital capacity.

While drug "tolerance" may develop to this

new compound, we have not encountered need for increased dosage during the course of this study.

We have found this new bronchodilator, Bronkometer, to be effective, convenient, well tolerated by the patients, and singularly free from central nervous system and cardiovascular side effects, even in hypertensive patients.

SUMMARY

A brief history of bronchodilator inhalation therapy has been presented and the chemistry and bibliography for a new bronchodilator combination, Bronkometer (isoetharine 0.6 per cent, phenylephrine 0.125 per cent, and thetyldiamine 0.05 per cent) have been reviewed. Results of treatment in 100 adult chronic asthmatic patients indicated good to excellent results in 89 per cent, with good patient acceptance. Laboratory and clinical observations of the cardiovascular system indicated singular freedom from side effects, even in hypertensive patients.

Bronkometer and Bronkospray proved valuable adjuncts to intermittent positive pressure breathing therapy.

Bronkometer and Bronkospray were supplied by Breon Laboratories, New York City.

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Primary Embryonal Rhabdomyosarcoma of the Anterior Mediastinum

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Minneapolis

PRIMARY RHABDOMYOSARCOMA of the mediastinum is a rare lesion. In a summary of mediastinal tumors, Schlumberger¹ stated that there were no rhabdomyosarcomas of primary origin in the mediastinum. He felt that there might be direct extension from surrounding areas into the mediastinum as from the diaphragm. In a review of the literature he could find no reports of this lesion of primary origin in the mediastinum with the possible exception of a report by Fox and Hospers.² However, their lesion was undifferentiated and gave origin to a liposarcoma and a rhabdomyosarcoma. It was possible that this lesion actually represented a malignant teratoma, but there was no evidence of epithelial elements and it thus might be better classified as a mesenchymoma.

It is, therefore, with interest that I followed a patient in whom a malignant lesion in the anterosuperior mediastinum developed and who succumbed within a few short months.

CASE REPORT

L. B. (SLPMC No. 26-985), a 25-year-old married white female, was first examined at the St. Louis Park Medical Center in 1955. There were no significant abnormal findings. A postero-anterior chest roentgenogram was interpreted as being "normal."

In 1958 she had a "routine" complete physical examination. Except for obesity the patient was in good health. There was no change in the chest roentgenogram.

In March 1961 the patient, then 31 years old, noted vague neck and shoulder distress unrelated to any recognized factor. She also had recurrence of mild abdominal distress suggestive of biliary tract disease. The history and physical examination were otherwise noncontributory. The roentgenographic studies of the gallbladder and the upper gastrointestinal studies

including an esophagram were interpreted as being normal. Similarly, a chest roentgenogram demonstrated no change from previous studies (figure 1). The patient received no specific therapy and all abnormal symptoms disappeared.

However, in mid-August 1961, the patient had a recurrence of vague chest distress, best described as a "sense of heaviness" in the precordial and substernal area. This sensation was present day and night and unrelated to any other factors. It was not severe and did not usually interfere with the patient's sleep or housework. Except for anorexia, the patient felt well. There were no abnormal respiratory symptoms. She did not smoke cigarets and was not on medications.

On September 1, 1961, a complete physical examination was within normal limits. The blood pressure was 130/80 mm. Hg and the body temperature 98.4° F. The urinalysis and hemogram were also within normal limits.

However, the anteroposterior chest roentgenogram depicted a marked change from the previous films (figures 2 and 3). Subsequent studies demonstrated that the mass was in the anterosuperior mediastinum.

The patient was hospitalized. On September 3, 1961, a left scalene fat and node removal was nondiagnostic on pathologic study. An exploratory thoracotomy was performed on September 7, 1961.

Exploration revealed the anterosuperior mediastinum to be obliterated by a grayish infiltrating neoplasm which had invaded the left lung, the pericardium, the hilus, and the retrosternal tissue. The origin of the neoplasm appeared to be in the anterosuperior mediastinum. After biopsy, the thoracotomy was closed. The biopsy demonstrated a malignant neoplasm. The patient recovered without difficulty.

Cobalt irradiation to the mediastinal neoplasm brought some improvement in the radiologic picture. However, the young woman had widespread bony metastasis evident by November 1961. She died January 13, 1962.

JEROME T. GRISMER is a thoracic surgeon associated with the St. Louis Park Medical Center and is on the staffs of Mount Sinai and Methodist hospitals, Minneapolis.

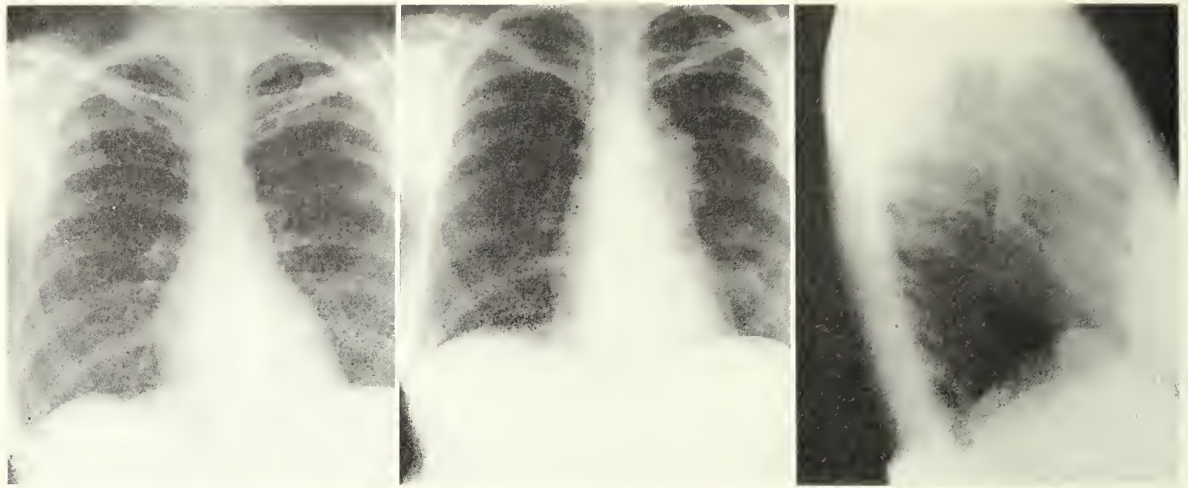


Fig. 1. (*left*) Normal chest roentgenogram made March 10, 1961. Fig. 2. (*center*) Chest roentgenogram, made September 1, 1961, demonstrating mass in left hilar area. Normal shadow of aortic arch is present. Fig. 3. (*right*) Left lateral chest roentgenogram, made September 1, 1961, portraying mass in retrosternal area of anterosuperior mediastinum

Autopsy demonstrated metastatic neoplasm of the lungs, liver, pancreas, kidneys, ovaries, stomach, small intestine, lymph nodes, and scalp.

DISCUSSION

The histology of the neoplasm was reviewed by a number of pathologists.³⁻⁶ One pathologist,⁶ in his discussion, reported that the neoplastic cells were "most likely a soft tissue sarcoma," but classified the lesion as "an undifferentiated malignant tumor." Three pathologists agreed that the lesion was of mesenchymal origin.³⁻⁵ It was also their independent opinion that this was an "embryonal rhabdomyosarcoma."⁴⁻⁶

This is an unusual neoplasm to be of primary origin within the mediastinum. Although the lung was also involved at the time of thoracotomy, it is my opinion that the neoplasm extended into the lung from the anterior mediastinum or the posterior surface of the anterior chest wall.

A review of the patient's previous "normal" chest roentgenograms fails to delineate any unusual shadows.

SUMMARY

The lesion diagnosed as an embryonal rhabdomyosarcoma and arising in the anterior mediastinum is reported. The rapidly fatal course of the disease was unchanged by cobalt irradiation therapy.

This study was supported in part by the St. Louis Park Medical Center Research Foundation.

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Notes from a Medical Journey

En route, Tbilisi (Tiflis)
to Moscow
18 September, 1961

Dear Jay:

Our Aeroflot jet drowns out talk (much noisier than our jets) as we fly north over the Caucasus after a fantastic week in Georgia. Dr. Paul White is writing notes in his journal and Margaret has curled up to sleep, so I'll start a thumbnail sketch of our stay in Tbilisi, travels through Georgia, and a weekend at Sukhumi on the Black Sea.

Today we had a big lunch with many toasts (the Georgians drink their local wine, the best in Russia) and then we started to worry about missing the plane. Roads were blocked for the arrival of the president of Cuba who was being given the works -- schools closed and Cuban flags everywhere. But our driver knew the back alleys and we were allowed to go on once we had slipped onto the airport road. As we were scrambling aboard the plane, a dozen of our Georgian friends arrived and then they stood around the plane on the ramp -- we standing at the open and unprotected forward door -- laughing and waving for half an hour while we waited for passengers who had been stuck in the Cuban "hero's" traffic snarl.

Last night we went by sleeper train from Sukhumi to Tiflis because weather canceled the evening plane. Margaret and I found ourselves in a 4-bed compartment with 2 Georgian men; but this was straightened out and eventually we were in a similar space with Dr. Paul White and Prof. Nodar Kipshidze, the Director of the new Institute of Therapy in Tiflis. Then the porter brought into the compartment a case of 12 bottles of Georgian wine, a present from our doctor friends in Sukhumi. We drank a bottle as the train started off and soon we were all sleeping as the train slid along on a remarkably smooth roadbed.

Morning brought its problems. The only "facilities" were a smelly W.C. at the end of the coach, and the idea is that each person is supposed to take the towel on his bunk to dry after a cold water wash.

Each of us, however, made the mistake of going to the little room early to respond to normal physiology, and by the time we got back to the compartment the porter (a husky middle-aged female) had departed with bed clothes -- and towels.

The purpose of our trip to Tiflis was to visit the new Institute of Therapy (patterned after that run by Dr. Myasnikov in Moscow) and to look into the question of the reputed great longevity of villagers in the Caucasus. The Institute is a 100-bed hospital and a laboratory building, the latter still in an early stage of construction. Dr. Kipshidze and his top staff of about 8 doctors seem to be competent and full of enthusiasm. They have decided to concentrate in 3 areas: cardiac diseases, liver disease, and bronchitis and emphysema. They already have the hospital operating, though research projects are not yet in full action.

We saw valvular and hypertensive heart disease patients but no clear-cut recent infarcts, though we were told that coronary heart disease is fairly common. One man in his 30's carried a tentative diagnosis of coronary heart disease with which we could not concur. He had a history of spells of atypical chest pains, lasting hours at a time, not associated with exercise, and not relieved by nitroglycerine. Blood pressure, electrocardiogram, blood studies, and chest roentgenogram were perfectly normal. After our discussion the doctors stopped talking about him as a "probable coronary."

The Institute of Therapy takes referred patients, presumably in the area of their interests, though the patient population was not greatly different from that of any medical department in a general hospital. Patient facilities are comfortable and the equipment is not bad as far as it goes; presumably it will be much more complete when the lab building is finished. An open-heart surgery unit is planned, but we learned no details. They do no surgery now, but mitral valve and patent ductus operations are done at another hospital in town.

En route to Sukhumi we stopped at Saltubo, a mineral water spa with a dozen hotel-like units, each with a capacity of 300 to 400 ambulant patients or people sent there for a rest with some medical attention. Bedrooms, some for couples with sitting room attached, are cheerful and look out over a great park-like area with views of the mountains. Each building has pleasant dining rooms, a theater (movies and concerts alternate), recreation rooms, verandas for taking the sun, physical therapy facilities, and a dental clinic. Patients come from all over Russia and it is completely free for those sent by medical referral; others pay the equivalent of a dollar or two daily for the three-week "cure." Saltubo is always full and several large new units are in construction.

On admission each patient has medical and dental examinations. Some bring documentation from their referring physicians, but mostly this is pretty scanty. A dietitian prescribes one or another diet (the food looked pretty good), everyone has a schedule for the bath, and some have additional physical therapy of a simple kind. The dentists are busy. With a three-week stay each dentist has an average of only about 20 minutes for each patient.

The doctors at Saltubo attribute wonderful things, especially for rheumatic patients, to the radioactive mineral water. The whole atmosphere, including the decor, resembles the old spas of Central Europe before World War II. The Tiflis doctors with us smiled about the Saltubo water, but they and we agreed that the rest and change in pleasant surroundings help many people.

This letter threatens to be too long so I'll try to continue about the monkey colony and the old men when I have time in the next few days. A bit ago, we passed up the Aeroflot tray dinner in hope of something better to eat in Moscow. Incidentally, the air hostesses are amiable but obviously not selected for youth and beauty. The fact that they have no uniforms and seem to shop in bargain basements does not help.

Now we are apparently power-diving (Russian style) for the Moscow Domestic Airport; the seat belt sign is on but people are walking in the aisles and pushing toward the exit.

All the best,

As ever,

A handwritten signature in cursive script, reading "Ancel Keys". The signature is fluid and elegant, with a prominent loop at the end of the last name.

Ancel Keys

AK/ji



Stanley Robert Maxeiner, M.D.

HENRY E. HOFFERT, M.D.

Minneapolis

STANLEY Robert Maxeiner was born in Chippewa Falls, Wisconsin, on June 17, 1885, the son of John R. and Clara Stanley Maxeiner. After graduation from the Chippewa Falls high school in 1903, he entered the University of Minnesota where he successfully completed his premedical and medical school training. He interned at the Minneapolis General Hospital in 1909.

In 1910 Dr. Maxeiner joined the surgical practice of Dr. Robert Emmet Farr, an association which was to last until 1923 and which left an indelible imprint on him. First as assistant, then as associate, and later as a partner, he collaborated with Dr. Farr in the development of local and regional anesthesia. Dr. Maxeiner did much of the research and cadaver dissections for Dr. Farr's book on this subject. Probably because many of their surgical procedures were done under local anesthesia, he developed a gentle touch, a tremendous respect for human tissue, and the ability to make most surgical procedures accurate anatomical dissections. He also learned the value of keeping up with medical and surgical literature, of attending conferences and conventions regularly, and of making contributions of his own whenever he was able to do so.

Dr. Maxeiner entered the military service in June 1917 as a captain in the medical corps attached to the British Expeditionary Forces and spent sixteen months in the front lines in France. He suffered an eighth nerve deafness from shell concussion which resulted in permanent deafness in his right ear. Although this condition was an aggravation to him, he never allowed it to affect in any way his par-

ticipation in the activities in which he became interested.

He served as attending surgeon at the Minneapolis General Hospital for seven years and, with the organization of the United States Veterans Hospital, became attending surgeon and surgical consultant, a position which he held for over thirty years. These two appointments enabled him to engage in clinical research and in teaching younger men in the field of surgery. No easy man this: he demanded of his students industriousness, dedication to duty, and willingness to work long and patiently to acquire an adequate knowledge and proficiency and technic in their chosen profession. The success with which he carried out assignments is attested by the respect and gratitude tendered him by the many younger surgeons who came under his influence.

Always intensely interested in organized medicine, he belongs to many professional organizations in all of which he has made definite contributions. He is a member and past president of both the Hennepin County Medical Society and the Minnesota State Medical Association, a founder and past president of the Minneapolis Surgical Society, a founder and first president of the Minneapolis Clinical Club which later became the Minneapolis Academy of Medicine, a member of the Minnesota Academy of Medicine and the Western Surgical Society, and a fellow of the American College of Surgeons and the International College of Surgeons. He is a charter member of the American Board of Surgery.

He was appointed clinical assistant professor of surgery at the University of Minnesota in 1930, clinical professor of surgery in 1949, and, a few years ago, emeritus clinical professor of surgery.

Dr. Maxeiner has always been eager to share his

HENRY E. HOFFERT is in surgical practice in Minneapolis.

experiences with others—in “off the cuff” talks as well as in more formal contributions to medical and surgical literature. His 28 published articles cover a wide range of subjects. As a practitioner, he finds no task too small, no problem too big; he is always willing to lend an attentive ear; and he is always eager to extend a helping hand—these are some of the characteristics which have endeared him to his patients, friends, and professional colleagues.

Despite a busy professional life, he has found time to engage in many civic and social endeavors. He has been active in Kiwanis for over forty years and is a member of the Civic and Commerce Association. He also maintains memberships in the Minikahda and Lafayette clubs.

His hobbies are golf and hunting, although he also enjoys the symphony and opera a great deal.

In golf he was a low handicap player for many years and his ability as a hunter might be demonstrated by a recent feat in which he brought down 7 ducks with 3 shells in less than five minutes.

In 1922, Dr. Maxeiner married Madeline Teas Wood, who has been his devoted companion, enthusiastic supporter, and constructive critic. They have two sons, William H. Wood and Stanley Robert Maxeiner, Jr., and 7 grandchildren.

After a full life, Dr. Maxeiner's greatest satisfactions come from seeing many of his patients with long survivals after surgery for malignant disease; the successes of the younger men who have worked under his guidance, especially his many junior associates; and, more recently, the acquiring of professional stature by his son S. R. Maxeiner, Jr., who is associated with him in the practice of surgery.

PERSISTENT OR RECURRENT SYMPTOMS after removal of the gallbladder may be due to other diseases or to functional disturbances of the biliary tract. Visualization of the extra hepatic biliary tract by intravenous cholangiography will provide an accurate diagnosis in most instances and may prevent useless reoperation. The most common organic cause of symptoms is choledocholithiasis. The stones generally are visible on a good cholangiogram. Gas in the ducts makes an accurate diagnosis virtually impossible. However, errors are few and surgical findings at reoperation usually confirm the cholangiographic diagnosis. A dilated common duct does not invariably indicate further disease. Enlargement may be due to distal obstruction or may mean merely that a previously obstructed duct has not returned to normal size. A cystic duct remnant may be a site of stone formation, but if neither stones nor pathologic change can be seen, it is unlikely to give rise to symptoms. Both normal and abnormal biliary tracts were well visualized by cholangiographic examination after cholecystectomy in 824 of 956 patients. The majority of cases of nonvisualization were probably due to biliary obstruction or impaired hepatic function.

RICHARD J. BEARGIE, JOHN R. HODGSON, KENNETH A. HUIZENGA, and JAMES T. PRIESTLY: Relation of cholangiographic findings after cholecystectomy to clinical and surgical findings. *Surg., Gynec. & Obst.* 115:143-152, 1962.

Transactions of the North Dakota State Medical Association

SEVENTY-FIFTH ANNUAL MEETING
Bismarck, North Dakota, June 2, 3, 4 and 5, 1962

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SPECIAL SESSION

House of Delegates

A special session of the House of Delegates of the North Dakota State Medical Association was called to order by the Speaker of the House, Lee A. Christoferson, M.D., at 2 p.m., September 24, 1961, at the Prince Hotel, Bismarck.

Dr. E. G. Vinje, chairman of the Credentials Committee, reported there was a quorum present and credentials were in order.

Secretary Buckingham called the roll. The following delegates and alternates were present: Drs. A. C. Burt, Fargo; J. F. Houghton, Fargo; Henry A. Norum, Fargo; L. E. Wold, alternate, Fargo; J. F. Schneider, alternate, Fargo; J. H. Mahoney, Devils Lake; G. H. Hilts, alternate, Cando; G. L. Countryman, Grafton; Robert Painter, Grand Forks; Keith Vandergon, alternate, Grand Forks; C. B. Porter, alternate, Grand Forks; F. D. Naegeli, Minot; A. F. Hammargren, Harvey; B. Hordinsky, Drake; J. L. Devine, alternate, Minot; C. J. Klein, Valley City; Edmund Vinje, Hazen; Carl Baumgartner, Bismarck; M. A. K. Lommen, Bismarck; Milton Nugent, Bismarck; J. N. Elsworth, Jamestown; John Van der Linde, Jamestown; Dean R. Strinden, Williston; Norman Ordahl, Dickinson; W. C. Hanewald, Dickinson; Robert Hankins, alternate, Mott; and James Little, Mayville.

There were 20 delegates and 7 alternates present. The following also attended: Drs. J. D. Craven, G. W. Toomey, C. M. Lund, E. H. Boerth, C. H. Peters, C. J. Glaspel, Wm. Buckingham and Mr. Lyle Limond.

The reading of the minutes of the last meetings of the House of Delegates on May 6 and 7, 1961, was dispensed with, with the exception of 2 sections.

The first section dealt with the resolution made and passed concerning instructions to the Medical Economics Committee, as follows: "We recommend that the Kerr-Mills bill be supported and that the Plan A schedule of Blue Shield, minus 10 per cent, as a contribution by the medical profession, be applied."

The second section dealt with the report of the nominating committee, W. E. G. Lancaster, M.D., chairman, and specifically the names of the nominees for the Board of Medical Examiners to be submitted to Governor Guy for his selection. These were as follows:

1. For Charles Ameson, M.D., of Bismarck, whose 2 terms expire, the names of C. H. Peters, M.D., of Bismarck, and Rudolph Froeschle, M.D., of Hazen.

2. V. G. Borland, M.D., of Fargo, to succeed himself for another three year term.

3. Frank D. Naegeli, M.D., of Minot, to succeed himself for a full three year term.

Speaker Christoferson called upon Dr. Peters, a member of the negotiating team of the Committee on Medical Economics, who gave a résumé of the negotiations with the Welfare Board as concerns a fee schedule for M.A.A. The offer of the association for a fee schedule using Plan A schedule of Blue Shield, minus 10 per cent, was not accepted by the board, and the negotiating team requested that they be permitted to meet with the members of the Welfare Board at their next meeting. As an outgrowth of this meeting on August 23, the board instructed Carlyle D. Onsrud to secure an attorney general's opinion regarding section 28 (payment of services) of the M.A.A. statute. The association was unable to request such an opinion as the request must come from a state agency. A copy of the attorney general's opinion, as incorporated in a letter to Mr. Carlyle D. Onsrud,

executive director of the Public Welfare Board, dated September 13, 1961, follows:

"OPINION
State of North Dakota
Office of Attorney General
Bismarck
Leslie B. Burgum
Attorney General

September 13, 1961

Mr. Carlyle D. Onsrud
Executive Director
Public Welfare Board
Bismarck, North Dakota

Re: Medical Assistance for the Aged

Dear Mr. Onsrud:

This is in reply to your letter of September 1, 1961, concerning the above named topic.

You state the Public Welfare Board currently negotiated with the North Dakota State Medical Association and the North Dakota Hospital Association as to fees which the Public Welfare Board would approve for payment of medical and hospital care for any and all welfare cases for which medical and hospital care was authorized by the county welfare boards. These fees are to be allowed for General Assistance, Old Age Assistance, Aid to the Blind, Aid to Dependent Children, and Aid to the Permanently and Totally Disabled which, at the time negotiations were conducted, covered all of the categories of assistance and all of which were approved only on the basis of need.

The 1961 session of the Legislative Assembly enacted chapter 302 of the 1961 session laws which included an additional program of relief known as Medical Assistance for the Aged. The additional program of relief provided for medical needs to otherwise eligible applicants who do not have 'sufficient income or other resources to provide for necessary medical and hospital care and treatment.'

You further note the provisions of section 28 of chapter 302 of the 1961 session laws which provide:

"*Payment for services.* The public welfare board is authorized to negotiate to pay dispensers of medical services according to the usual and customary fees being charged in the local community for services rendered to persons of comparable economic status. Should the board contract with private agencies or carrier for all or part of such medical services, it is authorized to make payment direct to such agencies or carriers."

Based upon the facts and statutes, you ask the following questions:

"1. Is it mandatory that the Public Welfare Board negotiate with the Medical Association?

"2. Is there any legal reason why the Public Welfare Board must negotiate for a separate fee schedule apart from the other programs for the Medical Assistance for the Aged category?"

In reply to your first question, the provisions of section 28 of chapter 302 of the 1961 session laws authorize the Public Welfare Board to negotiate. In this connection we also note the pertinent provisions of section 3 of this Act:

"This Act shall be administered on a fee for services basis to dispensers of medical services, according to consistent regulations adopted for that purpose. The Public Welfare Board may contract with private agencies or carriers to cover part or all of the benefits specified herein, provided that no contract with a private agency or carrier shall deny the patient freedom of choice of doctor or hospital or other vendors of medical services."

The provisions of sections 28 and 3, quoted above, indicate it is not mandatory that the Public Welfare Board negotiate with the medical associations. These sections only provide authorization for such negotiation and contract. We have not seen the result of the negotiations with the North Dakota State Medical Association and the North Dakota Hospital Association and are, therefore, unaware of the provisions of any agreement which may have been entered into. However, we do not believe the state medical association, the state hospital association, or the Public Welfare Board is bound by any such agreement insofar as Medical Assistance to the Aged is concerned. We reach this conclusion because we presume that at the time the negotiations were entered into, Medical Assistance to the Aged was not considered. Since it was not a part of the negotiations, any fee schedule arrived at is not binding on any of the parties insofar as Medical Assistance to the Aged is concerned. If, of course, the agreement provides the schedule to be binding on all the parties as to any

future assistance programs, it would then include Medical Assistance to the Aged.

Our answer to your first question is: it is not mandatory that the Public Welfare Board negotiate with the Medical Association. However, as stated above, if no agreement is reached with the medical association, we do not believe the fee schedule adopted for other types of assistance is binding upon the medical association unless specifically provided for in such agreement insofar as Medical Assistance to the Aged is concerned. If agreement is not reached by negotiation, the Public Welfare Board must then pay as billed for services rendered, providing the bill is reasonable.

In reply to your second question, we refer in part to our reply to your first question. Unless further negotiations are entered into, we do not believe the medical association or the hospital association is bound by the existing fee schedule insofar as Medical Assistance for the Aged is concerned. It may well be that the existing fee schedule for other public welfare programs should also apply to the Medical Assistance for the Aged program. However, this is a matter of negotiation and agreement between the parties involved. We presume it would be advisable to have some form of agreement with the dispensers of medical services for Medical Assistance to the Aged, as well as for the other assistance programs. However, this is a matter of policy to be determined by the Public Welfare Department.

Apparently, the contention has been made that, due to the provisions of section 28 of chapter 302 of the 1961 session laws, the Public Welfare Board must negotiate with the dispensers of medical services and provide for a higher schedule of fees for recipients of Medical Assistance to the Aged than for the other categories of relief. With this contention, we cannot agree. Insofar as the higher fee schedule is concerned, section 28 does provide for the payment of "The usual and customary fees being charged in the local community for services rendered to persons of comparable economic status." We can find no provisions in the other assistance programs which require a fee less than the "usual and customary fees being charged in the local community for services rendered to persons of comparable economic status." We do not have any information or knowledge concerning the fees paid in the other assistance programs. It is possible that they are less than the usual and customary fees in that community. In such case the matter is open to negotiation between the Public Welfare Board and the dispensers of medical services. Whether the fees for other assistance programs are less than the usual and customary fees charged in the local community concerned is a question of fact and not one of law. However, we do not believe that the language of section 28 of chapter 302 of the 1961 session laws in and of itself requires a higher schedule of fees for recipients of Medical Assistance to the Aged than for the other categories of relief. As stated above, this is a question of fact and not one of laws.

We trust this will satisfactorily answer your questions.

Yours very truly,

(Signed) LESLIE R. BURGUM,
Attorney General"

It was felt that the press releases which appeared in various North Dakota newspapers did not state properly the facts as set forth in this opinion. Speaker Christoferson instructed the chairman of the Committee on Public Relations to get in touch with the chairman of the Medical Economics Committee to release the correct information to the press, and possibly give the attorney general's complete statement.

Upon receipt of the opinion, the negotiating team of the Medical Economics Committee requested of the Welfare Board that, following their meeting on September 19, a letter stating their decision could be forwarded to Dr. Peters, inasmuch as a special session of the House of Delegates was being held on September 24 to discuss the fee schedule for M.A.A. Such a letter from Mr. Onsrud, dated September 22, was received by Dr. Peters and contained the following motion: "That whereas the income of recipients of Medical Assistance for the Aged is not substantially different from those on Old Age Assistance, it is the opinion of the Board that the present rates for Old Age Assistance are reasonable for Medical Assistance for the Aged."

The welfare board has issued no new forms for the M.A.A. program. To determine whether a welfare recipient is under the M.A.A. program or not, one notes

the last 2 digits in the case number on the Medical-Health Service Authorization form received from the county welfare director. If the digits on the authorization end in 90, 91, 92, or any number in the nineties, this most likely signifies that the person is under the M.A.A. program.

Dr. Peters said that the Medical Economics Committee did not feel that the association should accept a fee schedule lower than Plan A of Blue Shield, less 10 per cent, since the M.A.A. program would cover a new segment of the population.

Dr. Peters also advised the House of Delegates that beginning on October 1, 1961, the Workmen's Compensation Bureau was issuing a new fee schedule, with charges the same as to private patients. The physician now may charge his customary fees.

Speaker Christoferson asked for open discussion. As a result, Dr. Porter made the motion that the previous resolution as adopted of Plan A Blue Shield, less 10 per cent, for the M.A.A. program, be rescinded. Motion seconded by Dr. Painter and carried.

The Chair next entertained a motion for instructions to the Medical Economics Committee for further negotiations. Dr. Lommen moved that the Committee on Medical Economics negotiate for a separate schedule for M.A.A. recipients. He stated he would accept an amendment. Dr. Nugent added the amendment that the House of Delegates instruct the Committee on Medical Economics to negotiate a schedule with the Welfare Board for M.A.A. recipients for less than Plan A Blue Shield, less 10 per cent. Until then, no schedule exists. Dr. Little seconded the motion, including the amendment, and the motion carried.

Dr. Peters said that in the interim the physician may submit any reasonable bill for the patient, and suggested that the statement "usual and customary fee" be typed on claim forms.

The committees on medical economics and public relations were instructed to inform the press and the Welfare Board of the action taken.

The Speaker instructed the executive secretary to send out a statement to all physicians concerning the action of the House, advising how the forms should be submitted.

Speaker Christoferson introduced Dr. E. H. Boerth, President of the Association. Dr. Boerth complimented the delegates on their attendance and interest. He stated he had received a letter from Governor Gny after the names of the nominees to the Board of Medical Examiners had been forwarded to him. Dr. Boerth met with the governor, who explained that he did not feel there was enough latitude in the choice of names. The names of Drs. Naegeli and Borland were acceptable, but not those of Drs. Peters and Froeschle. The governor stated he would like someone more liberal on the board. Dr. Boerth advised the delegates that he did not feel it was his prerogative to alter the decision of the nominating committee of the House of Delegates in session on May 7, 1961, and he directed a letter to W. E. G. Laneaster, M.D., chairman of that nominating committee. Dr. Laneaster, in turn, wrote to Governor Guy again, requesting that the names of Drs. Peters and Froeschle be considered. This second request to the governor met with the same answer, that the names were not acceptable. It was necessary for the House of Delegates to meet for the selection of new nominees.

Speaker Christoferson introduced C. J. Glaspel, M.D., who has acted as secretary of the Board of Medical Examiners for many years. Dr. Glaspel announced his res-

ignation effective no later than December 1, 1961, after a replacement has been selected. He reviewed briefly the duties of the secretary—many times disagreeable. The duties are time-consuming and cover a wide range. It is the responsibility of the secretary to reprimand physicians, on occasion, to explain to representatives from small town groups the difficulty of obtaining a physician for smaller towns, and to communicate with physicians who employ other physicians who are not licensed in North Dakota. He feels it is time to pass these responsibilities on to someone else.

Speaker Christoferson thanked Dr. Glaspel for his comments and called for a vote of confidence, which was given.

Dr. Lund was introduced and gave a résumé of the activities of the association during his year as president. He felt that much had been accomplished for the benefit of the association and the people of North Dakota, including the passing of the M.A.A. program, the appointment of a psychiatrist as the superintendent of the State Hospital at Jamestown, the appointment of a physician as State Health Officer, and also as a mental health authority.

He reviewed the appointments to the Board of Medical Examiners following the deaths of Drs. Halliday and Rodgers. The names of Drs. H. L. Reichert and V. J. Fischer were submitted to the governor. The Council was informed that the name of Dr. Fischer was not acceptable, so the names of Drs. Jacobson, Reichert, Fischer, and Naegeli were submitted. Drs. Reichert and Naegeli were appointed to the unexpired terms.

Concerning the current appointments to the Board for a replacement for Charles Arneson, M.D., Bismarck, whose 2 terms expired, the names of C. H. Peters, M.D., Bismarck, and Rudolph Froeschle, M.D., Hazen, were submitted, together with the names of V. G. Borland, M.D., Fargo, to succeed himself for another three-year term, and Frank D. Naegeli, M.D., Minot, to succeed himself for a full three-year term. The names of Drs. Naegeli and Borland were acceptable to the governor, but not the names of Drs. Peters and Froeschle. The governor stated he wished to appoint someone to the board with whom he could talk confidentially. Speaker Christoferson and Dr. Boerth met with Governor Guy, who asked for 3 more names.

Dr. Toomey was appointed chairman of the Nominating Committee, together with Drs. Painter and Naegeli. Since the committee had no authority to rescind the names of those nominees already chosen, it announced the addition of 3 more names to submit to the governor. These physicians are: Drs. E. H. Boerth, James Moses and Robert Nuessle. Dr. Christoferson asked for nominations from the floor, and Dr. Lommen nominated Dr. Cleary. A written ballot was taken from members in attendance, and a count made by Speaker Christoferson and verified by Secretary Buckingham. The names of Drs. Boerth, Moses and Nuessle were voted upon as those to be submitted to the governor for appointment to the Board of Medical Examiners. (An announcement was made some time later, through the press, that Governor Guy had appointed Dr. Robert Nuessle to succeed Dr. Arneson.)

Speaker Christoferson announced that the next meeting of the House of Delegates would be held in Bismarck June 2-6, 1962.

The motion of adjournment was made by Dr. Countryman, and the meeting adjourned at 4:30 p. m.

PROCEEDINGS of the House of Delegates of the North Dakota State Medical Association Seventy-Fifth Annual Meeting

The First Session of the House of Delegates of the North Dakota State Medical Association was called to order by the Speaker of the House, Dr. Lee Christoferson, at 3 p.m. in the Prince Hotel, Bismarck.

Dr. Countryman, chairman of the Credentials Committee, reported a quorum present and credentials in order.

Secretary Buckingham called the roll. The following delegates and alternates responded:

Drs. A. C. Burt, Fargo; G. Howard Hall, Fargo; J. F. Houghton, Fargo; F. M. Melton, Fargo; H. A. Norum, Fargo; D. G. Jaehning, alternate, Wahpeton; G. H. Hiltz, Cando; G. W. Seibel, New Rockford; R. C. Painter, Grand Forks; R. E. Mahowald, Grand Forks; G. L. Countryman, Grafton; W. C. Dailey, alternate, Grand Forks; C. B. Porter, alternate, Grand Forks; B. Z. Hordinsky, Drake; G. R. Richardson, Minot; L. A. Giltner, Minot; C. E. Jensen, Valley City; P. O. Dahl, Bismarck; Carl Baumgartner, Bismarck; M. E. Nugent, Bismarck; R. B. Tudor, Bismarck; M. A. K. Lommen, alternate, Bismarck; J. N. Elsworth, Jamestown; A. F. DuMais, alternate, Jamestown; N. B. Ordahl, Dickinson; W. C. Hanewald, Dickinson; J. M. Little, Mayville.

There were 22 delegates and 5 alternates present. The following also attended the House of Delegates meeting:

Drs. T. E. Pederson, C. H. Peters, E. J. Larson, W. A. Wright, L. W. Larson, R. W. McLean, G. W. Toomey, Keith Foster, O. A. Sedlak, C. M. Lund, E. H. Boerth, R. D. Nierling, C. J. Glaspel, Amos Gilsdorf, V. G. Borland and F. D. Naegeli, and Mr. Lyle Limond and Mr. Daniel Buchanan.

Dr. Richardson from Minot stated that Dr. Jens Sahl, Jr., was in the House of Delegates as an alternate to Dr. Garrison in the Minot delegation. Dr. Christoferson said that all dues had not been sent in from the Fourth District Society. It was entitled to seat only three delegates and these three already were seated.

Dr. Christoferson asked members to stand for a moment of silence out of respect for eight valued members who died during the past year.

The motion was made, seconded, and passed that the reading of the minutes of the last session be dispensed with and that they be accepted as printed in *THE JOURNAL-LANCET*.

Dr. Christoferson asked Dr. D. M. Lawrence to introduce Dr. Richard Prouty, State Toxicologist. Dr. Lawrence's remarks follow: "I welcome this opportunity to make a few comments about the new State Toxicology Laboratory at Fargo. Some of you know the conditions prior to obtaining it. Pathologists, involved in regular medical work, were reluctant to take on this work. None was available in the state and I was advised by pathologists and state's attorneys so see if there were any available elsewhere. I contacted the State Crime Bureau in St. Paul and it informed me the legislature had curtailed funds so it could not take care of these matters from the Twin Cities. We managed without this service for several years but it was awkward. In 1959 the Medical Service of the University of North Dakota at Grand Forks informed us that personnel was not available there. That same spring, this House of Delegates passed a resolution to investigate the need for and the possibility of establishing such a laboratory. As a result, in 1961 the legislature appropriated funds. The office was established in October 1961, and we were fortunate to procure the services of Dr. Richard Prouty. He was appointed State Toxicologist.

He has had very little demand for his services from other areas of the state. We feel this may be due to the

fact that many physicians in other areas are not familiar with the procedures necessary to obtain services, or they do not know the laboratory exists. I prevailed upon Dr. Christoferson to bring this matter before you, for if this laboratory is not used the next legislature may not appropriate funds and we will lose it. I would like to see it continued and used more.

I would like to introduce Dr. Prouty, who will explain the services and how to obtain them. He received his degree in chemistry in Alabama and became director of one of the laboratories there. From January 1955 to 1958 he was the Director of Toxicology, Army Research Laboratory in Tokyo, Japan. He then enrolled in Baltimore, Maryland, in Forensic Toxicology and remained there until October 1961 when he was appointed State Toxicologist for North Dakota."

Dr. Prouty's remarks follow: "I would like to thank Dr. Christoferson and all of you for giving me a few minutes of your time today. I would like to describe briefly what I have established in the way of laboratory service in toxicology for the people of North Dakota.

I also am obligated to you for my presence in the state. Your group was the primary motivating force which stimulated interest in the passage of the law creating this toxicology laboratory.

My quarters are in the basement of the Pharmacy building of the North Dakota State University in Fargo. I am fortunate in having enough space. I hope we will be able to stimulate more interest through physicians and medical treatment facilities in these services so that they will be utilized more.

The law stated that the laboratory would provide a service to all individuals or any political subdivisions within the state. The Bill was brief and not too explicit in defining the duties of the toxicologist. I had to draw up an operational policy and define what I would do and for whom. I have these procedures mimeographed and would like all of you to receive copies. My address is the State Toxicology Laboratory, North Dakota State University, Fargo.

The service is a diagnostic one in the detection of poisoning. Any medical facility may request service.

I am somewhat limited in cost of services. This is a one-man show at present. However, if I am not equipped to do the service, I will be happy to entertain your request, and will try to borrow the needed implements.

The law stated that I must establish a schedule of fees. There was some resistance to this new service, so there was a desire to show there would be money coming back to the state to help defray expenses. I have not worked in any laboratory except a state or county service and I am not experienced with fees. However, as I understand it, these fees are to go back to the State General Fund. I obtained a list of fees charged by three of the largest privately owned toxicology laboratories in the United States. I averaged them and took a third of this figure. I feel there should not be a fee for this service. However, in setting one, I wanted it high enough to discourage needless requests but low enough to take care of needy requests.

To date the services have not been utilized as much as they should have been. There have been several cases in the state of poisoning and resulting deaths but there have been no toxic analyses. I have notified every attorney and coroner about our laboratory, but I could carry in two hands the number of cases I have received from the other areas of the state. I hope you will advise the various individuals in your areas of the services. If these services are not utilized more completely, I will not be

able to get additional funds to continue. If the legislators do not see enough cases given service by this laboratory, they might decide this money could be used elsewhere.

We have made one advance through the cooperation of the State Highway Patrol and the State Health Department. I have succeeded in getting a chemical test program for intoxication throughout the state. When I came here these blood tests were being done at different laboratories and a number of methods were being used. Most of them, I am convinced, had inadequate controls. I believe the chemical test for intoxication was quite inadequate. All blood tests now will be done at our laboratory, where the method I use is satisfactory. I am working in conjunction with the state law enforcement agencies and the patrolmen. The program can be only as good as the testing facilities offered.

I thank you for the opportunity to appear here. With your cooperation and that of the law enforcement agencies, we can have a good toxicological service for North Dakota."

Dr. Christoferson welcomed Dr. Prouty to the state and will instruct the Committee on Public Health to investigate ways and means for utilizing this service.

He introduced Mr. Charles Johnson of the American Medical Association and Mr. William Daner, its legal counsel.

Dr. B. J. Clayburgh of Grand Forks spoke briefly on AMPAC and COMPACT.

Dr. Christoferson asked to refer the president's report to the proper reference committee. He also asked that reports of the secretary, treasurer, executive secretary, chairman of the council, councillors, special committees, standing committees and delegate to the American Medical Association, Medical Center Advisory Council and Governor's Health Planning Committee be referred to appropriate reference committees.

Dr. Christoferson announced the following appointments: Dr. C. B. Porter, member of Reference Committee No. 1; Dr. Norum, chairman, and Dr. Hordinsky, vice-chairman of Reference Committee No. 3; Dr. Countryman, chairman, Dr. Giltner, vice-chairman, and Drs. Jaehning and DuMais, members of Reference Committee No. 4; and Drs. M. A. K. Lommen and W. C. Dailey, members of Reference Committee No. 5.

REPORT OF THE PRESIDENT

The activities of the state association will be detailed in reports in the Handbook. However, I would like to comment on a few important items.

It has been my pleasure during the year to attend several district society meetings. They were well attended and the membership exhibited an interest in the affairs of the state society as well as their own. The councillors seem to be keeping members informed on the scope of our activities. This is essential in maintaining continued and increased interest in state society activities.

Last year questionnaires were sent to members to determine on which committee they wished to serve. It was gratifying to have so many questionnaires returned. First, second or third choices were listed. It is natural that some committees were preferred over others, but with the excellent help of Mr. Limond and Mrs. Fremming, appointments were made to cover the various areas of the state. The committees worked well and I wish to thank the chairmen and members. Meetings have been well attended, and it is a tribute to the association when its members expend time and money in order to keep its various functions at a high level.

Shortly after the annual meeting in 1961, a meeting

was held in Jamestown of representatives of the North Dakota and South Dakota associations and their women's auxiliaries to plan for the combined annual meeting this June. The Committee on Scientific Program is to be congratulated on securing outstanding speakers. Mr. Limond and I were present at the South Dakota State Medical Association's annual meeting in Sioux Falls and had the opportunity of extending an invitation to come to Bismarck to help us celebrate our diamond jubilee.

Last June the entire state was honored when Dr. Leonard W. Larson was installed as president of the A.M.A. Several North Dakota physicians were at the meeting in New York and were privileged to be present at his inauguration. Some 900 attended the reception given by the North Dakota State Medical Association. It is gratifying to know that Dr. Larson is held in high esteem by members of the medical profession and laymen throughout the nation.

One of the annual highlights in North Dakota medicine is the North Central Medical Conference. The November meeting this year was well attended, and several North Dakota physicians were present. The president of the conference for the coming year is our own Dr. Tom Pederson. It is hoped that many North Dakota physicians will attend the conference next November. One of the topics on the program dealt with new legislation permitting physicians to incorporate. It was discussed by attorneys from Wisconsin, Minnesota, and South Dakota. The Legislation Committee of the North Dakota State Medical Association is considering legislation for North Dakota physicians. Another topic on the program was AMPAC. It is gratifying to note that the legislative committee has been active in the field of medical political action, as will be noted in Dr. O. W. Johnson's report.

It is extremely important for physicians to be interested in political issues and public affairs. AMPAC was organized to meet the need of providing the medical profession with an opportunity to assume a more active and effective role in public affairs. AMPAC helps its members to understand political issues and organizes them as an effective political action group. Since AMPAC is not bound by party labels, each physician should be a member of AMPAC in order to have his own interests protected and to support programs designed to obtain good government. Official recognition of AMPAC has been given by the Council of the State Association, and a group of spirited physicians, recognizing the need for both state and national medical political action committees, have organized to stimulate physicians in individual participation.

I attended the first A.M.A. Institute August 31 and September 1 held in Chicago. Mr. Limond and Dr. James Mahoney, chairman of the Public Relations Committee, also attended. The Institute is an expanded inter-divisional conference replacing the A.M.A. Public Relations Institute of previous years. Reports were given on medical society efforts in community action, disciplinary programs, expanded A.M.A. programs in drug information and other scientific activities, individual experiences in countering criticism from radio, TV, and the press, youth fitness, disaster medical care, and the A.M.A. "image." This was an inspiring meeting, and I can foresee further meetings as being equally good, if not better. Dr. Mahoney will comment on this in his Public Relations Committee report.

The association is fortunate in having secured the services of Mr. Daniel Buchanan to assist the association in its public relations and communications activities. Although he has served for only a short time, it can be

seen that he has potential. He has been well received at the meetings he has attended, and will be a big help in carrying out the wishes of the Public Relations Committee.

The Medical Economics Committee has been active during the past year and I have been privileged to attend its meetings. I refer you to the full report in the Handbook. In July 1961, some of the committee's members met with the Workmen's Compensation Bureau and an upward revision of fees was obtained. It is a pleasure to meet with its board members because of their co-operative attitude. I regret that a similar attitude is not present when the state association has to deal with some other state agencies.

The Advisory Committee of the State Welfare Department has met several times to smooth out problems of the department in an attempt to improve the relationship of the department with physicians throughout the state. However, all has not gone well with the Medical Economics Committee's effort in negotiating with the State Welfare Board in establishing a fee schedule for the new MAA program. The Welfare Board holds the view that MAA recipients and OAA recipients are the same, in spite of a ruling by the state Attorney General to the contrary. Since the board does not wish to negotiate a fee schedule, the Medical Economics Committee, supported by the Council of the State Association, had no alternative but to abrogate all fee schedules existing between the physicians and the Welfare Department.

In May 1961, a letter was directed to the Hon. Wilbur D. Mills, chairman of the House Ways and Means Committee, requesting time for one of our members to appear before his committee during the hearings on HR 4222 (King-Anderson bill). On July 27, 1961, Dr. C. H. Peters appeared and offered testimony opposing the bill. Each member of the association has received a copy of his excellent presentation. He deserves the thanks of the association for taking the time to appear in Washington on behalf of organized medicine. Several members have spoken to lay groups in the state, voicing their opposition to the bill. They also deserve thanks. There is no need in North Dakota for legislation such as this bill, since the state association has promoted and secured passage of the Kerr-Mills law to give medical aid to the indigent aged. The staff of the A.M.A. is to be commended for their efforts in helping the association when called upon in legislation as well as other matters. Blue Shield and commercial insurance carriers deserve credit for efforts in extending benefits to persons age 65 and over.

Efforts have been made during the year in soliciting the support of various organizations in our opposition to legislation that is detrimental to the medical profession. Resolutions opposing the King-Anderson bill have been received from the North Dakota Junior Chamber of Commerce, North Dakota Bankers Association, Chamber of Commerce, and the North Dakota Pharmaceutical Association. Several other groups have rallied to our side. It is to our interest to have various organizations allied with us, and we should not only expect help from them when we need it but help them when we are called upon to preserve the system of free enterprise and oppose socialistic tendencies.

For several years the state association has urged the securing of a doctor of medicine to head the State Health Department. This has been accomplished and we welcome Dr. Roy Amos, the choice of the State Health Council for this post. Through the efforts of the state association, a doctor of medicine is again the superintendent of the State Hospital at Jamestown. Dr. Ernst

Schmidhofer, the new superintendent, is a welcome addition to the state society.

The help I have obtained from the state office has been invaluable. I wish to express my most sincere appreciation and thanks to Mr. Limond, our most efficient executive secretary. His help and counsel during this year will be long remembered. He is deeply devoted to the welfare of organized medicine, not only at the state level, but from a national standpoint.

When you chose me as your president last year I was honored. It has been not only a privilege but a pleasure to have represented you at state and national meetings. I am grateful for the opportunity you have given me to serve.

E. H. BOZEMAN, M.D., President

REPORT OF THE SECRETARY

The following report of the secretary is respectfully submitted:

MEMBERSHIP: The total membership for 1961 was 466. Of this number, 435 paid the regular membership fee, 1 paid one-half year's dues, 3 were on a limited basis, and 26 were honorary members. One member was carried on a complimentary basis because of military service. Eight members died during the year, and several have left the state. New members, however, are being added steadily to our roster.

Table 1 shows the annual membership for the past 5 years:

TABLE 1
COMPARISON OF ANNUAL MEMBERSHIP

	1957	1958	1959	1960	1961
Paid memberships	395	403	418	418	436
Honorary memberships	18	16	24	24	26
Limited and retired	9	9	4	5	3
Dues cancelled (military service and age exemption)	6	5	2	4	1
	428	433	448	451	466

Table 2 shows the annual dues payments according to the cutoff date for preparation of this report for the past five years. Because of the lateness of the annual meeting this year, the cutoff date was extended. This gave members a grace period of two months in which to pay current dues, even though the Constitution and By-Laws state that all assessments must be forwarded to the secretary not later than March 1 of each year. Even with the extension of time, quite a large number of members are delinquent in payments.

TABLE 2

	April 15 1958	April 15 1959	April 13 1960	April 17 1961	May 1 1962
Paid-up members	313	309	335	348	374
Honorary members	16	20	22	27	25
To be honorary	3	4	5	2	2
Dues cancelled, military service	3	3	2	2	1
Limited		1	2	1	
Retired	3	1	1		
Totals	338	338	367	380	402

STATE ASSOCIATION MEMBERSHIPS

1961—Total Membership 466

District	Regular	Retired	Limited	Comp.	Honorary
First	91			1	2
Second	29		1		2
Third	75				4
Fourth	66		1		2
Fifth	10				1
Sixth	76				8
Seventh	34		1		3
Eighth	21				
Ninth	23				4
Tenth	11				
	436		3	1	26

1962—Total Membership 400

District	Regular	Retired	Limited	Comp.	Honorary
First	89				2
Second	28				1
Third	65			1	4
Fourth	38				3
Fifth	8				1
Sixth	67				7
Seventh	35				3
Eighth	17				
Ninth	19				4
Tenth	8				
	374			1	25

A.M.A. GENERAL MEMBERSHIPS

	1961	May 1, 1962
First	92	89
Second	32	29
Third	78	70
Fourth	69	41
Fifth	11	9
Sixth	81	72
Seventh	37	38
Eighth	21	17
Ninth	25	21
Tenth	10	8
	456	394

On April 19, 1962, a letter was directed to all secretaries of the district medical societies, advising that representation in the House of Delegates is based on 1 delegate for each 15 paid-up members or major fraction thereof. Delegates from the societies should be seated on this basis, so it is essential that dues be forwarded promptly. If the figure of 436 as shown in the 1961 chart of paid, active memberships is used as a guide, you will note that on May 1, 1962, 62 members were delinquent in dues payments.

The continued cooperation of all members will be greatly appreciated.

W. M. BUCKINGHAM, M.D., Secretary

REPORT OF THE EXECUTIVE SECRETARY

GENERAL COMMENTS: Your executive secretary attended several state, regional, and national meetings in behalf of the association.

This year we celebrate the 75th birthday of the association. Your executive secretary began his eleventh year

February 18, 1962. Mrs. Margaret Fremming, office secretary, began her twelfth year with the association. Mr. Daniel E. Buchanan, director of communications, came to us October 1, 1961.

The routine of the office shows an increased tempo as each year passes. This increase is due to more emphasis in the areas of medical economics, legislation, medicare, public relations, State Board of Medical Examiners duties and general services to the members. Part-time help has been necessary this past year.

LEGISLATION: We are in an all-out fight to keep medicine free in this country. Our greatest efforts have been directed toward the defeat of the King-Anderson bill (H.R. 4222). Dr. C. H. Peters of Bismarck testified against the bill before the House Ways and Means committee in Washington, D. C., during the latter part of July 1961. The Kennedy administration is exerting tremendous pressure to secure its passage.

PUBLIC RELATIONS: The following remarks are inserted by Mr. Buchanan, Director of Public Information and Education, with the approval of the executive secretary:

"Since October 1, 1961, when my employment by the executive committee of the council became effective, I have been gaining insight into the workings of organized medicine on the district, state and national levels. Much of my activity has been directed toward learning about the structure and functions of these units. This learning process will continue as a day-by-day endeavor.

Eight months' experience with an association now marking its diamond jubilee cannot qualify one as an authority on what North Dakota medicine can or must do to maintain good relations with the public where they exist and to build and improve relations where they are something other than favorable.

With these two criteria in mind, the following is submitted for consideration:

1. The Committee on Public Relations be changed to the Committee on Communications. The term public relations is nebulous, at best, and it is but one phase of the communication process.

2. A Committee on Communications could well be composed of physicians knowledgeable in areas such as medical economics, legislation, medical education, mental health, school health, so that collectively the committee could develop avenues through which to communicate the whole philosophy of the State Medical Association, both within and outside the profession.

Organized medicine in this state has nothing to hide. But a public cannot hold physicians and their professional associations in the high esteem that both deserve when the same public is being saturated by half-truths, misinformation and outright false accusations directed toward a great profession. Those who would downgrade medicine through the 'something-for-nothing' philosophy must come to grips with it through effective and sustaining communication. Let your lamp shine!"

Several members have accepted speaking engagements before groups and have explained ideas concerning care for the aged.

We have used paid advertising to draw the attention of the public to television and radio programs about the King-Anderson bill.

Several district societies have started an institutional advertising program in newspapers.

The Annis film has been sponsored by district societies over television and at meetings.

Thousands of pieces of educational material have been mailed from doctors' offices on the King-Anderson bill.

The pharmacists of North Dakota also have aided greatly in distributing this educational material.

Speakers' bureaus are being formed on the district level.

Our relationship with Blue Shield remains strong in the area of public information and education. It should grow stronger as time passes and if Medicine is to remain free in this country.

PHYSICIANS' PLACEMENT SERVICE: This office continues to give service to communities and medical groups seeking physicians.

U.N.D. MEDICAL SCHOOL SCHOLARSHIPS: The 1961 winners of the association's scholarship prizes (totaling \$500) offered at the school of medicine were as follows: anatomy, James Jarrett; physiology and pharmacology, microbiology, and pathology, Reed Keller; highest scholastic average, first year, Donald Wells.

FINANCE: The treasurer's report continues to show an improved balance. The goal of having one year's operating budget in reserve was maintained last year when you consider the certificates of deposit in the headquarter's office account. It is hoped this reserve can be kept at this level, in the interests of good business practice.

Receipt of dues continued to be slow, as noted in the secretary's report.

MEDICARE: The Dependents' Medical Care Program (Medicare) commenced on December 7, 1956. Up to January 1, 1962, 5619 claims had been processed by this office. The total sum paid to North Dakota physicians as of December 31, 1961, amounted to \$426,077.00. Each claim averages \$75.83.

THOUGHTS FOR THE FUTURE:

1. In our public relations program, thought must be given to securing allies in combating the continued growth of the Welfare State philosophy.

2. Interest should remain high in the field of national legislation affecting organized medicine.

3. As citizens, we must take a greater interest in and play a more active part in politics, beginning at the grass roots level. This is an important election year.

ACKNOWLEDGEMENTS: I wish to express sincere appreciation to President Boerth for his efforts in behalf of this association. Dr. Boerth made many trips in and out of the state on association business.

My sincere thanks also go to members with whom I worked this past year on committee assignments and other programs of the association.

LYLE A. LIMOND, Executive Secretary

REPORT OF THE CHAIRMAN OF THE COUNCIL

The Council of the North Dakota State Medical Association held its regular spring meeting May 6 and 7 at the Gardner Hotel in Fargo. The regular interim meeting was held on December 9 at the Gardner Hotel.

The first session of the spring meeting convened at 10 a.m., May 6. All councillors were present. Others present were: Drs. E. H. Boerth, W. A. Wright, C. M. Lund, E. J. Larson, W. M. Buckingham, R. H. Waldschmidt, and Mr. Lyle Limond.

The financial statement of the treasurer was discussed. Drs. E. J. Larson and R. D. Nierling agreed to review the schedule of U. S. government bonds and check into the possibility of re-investing bonds close to maturity.

In order to help meet additional expenses for the state meeting in 1962, a slight increase in the cost of booth space to the commercial exhibitors was established.

The problem of delinquent dues was discussed. It was decided to remind delinquent members by a statement signed by the president.

Dr. P. H. Wontat, Grand Forks, was asked to check into the possibility of finding some solution to the problem of getting more of the teaching staff of doctors at the medical school to affiliate with the association. Dr. T. E. Pederson was asked to check into the status of doctors practicing at the State Hospital in Jamestown.

A letter from Dr. M. C. Collins of the Medic Alert Foundation in California was read. It stated that the identification symbols of the foundation are a practical, useful, and valuable method of identifying patients with allergies and contraindications for medical care. A motion was made and carried that the letter be referred to the appropriate reference committee of the House of Delegates for action.

The council adjourned at noon and reconvened at 1:30 p. m.

It was reported that the position of Director of Public Information and Education was vacant, Mr. George Michaelson having resigned. Dr. J. H. Mahoney, chairman of the Public Relations Committee, discussed the problem. Mr. Don Eagles of Blue Shield answered questions regarding the public relations program as it affects Blue Shield. A motion was made and carried that the association continue the relationship that it has had this past year with Blue Shield and that it find a replacement for Mr. Michaelson.

The problem of Medicare contracts was discussed. Dr. Peters was requested to sign under protest new contracts with the underwriting director of Medicare, administered by the State Medical Society of Wisconsin.

Dr. W. A. Wright, delegate to the American Medical Association, discussed A.M.A.'s experience with public relations. The session adjourned at 3:30 p. m.

The second session was called to order at 5 p.m., May 7. All councillors were present. Others attending were Drs. E. H. Boerth, A. R. Gilsdorf, W. M. Buckingham, R. D. Nerling, and Mr. Lyle Limond.

The date for the interim meeting at Fargo was set for December 9, 1961. A motion was made and carried that an application for membership in the National Society for Medical Research be filed and that a check for \$25 to cover dues accompany it.

The House of Delegates requested the council to look into an incomplete Blue Cross Survey concerning hospital cost and utilization. The secretary was asked to write Blue Cross and urge that it be completed.

Acting on instructions from the House of Delegates, a committee was named to select a "practitioner of 1961." His name should be submitted to the A.M.A. not later than November 1961. The House of Delegates of the American Medical Association later discontinued this program, so the committee did not select a candidate.

Acting on instructions from the House of Delegates, each councillor was urged to promote establishment of a claims committee in each district to process controversial claims from Blue Shield and insurance companies.

Dr. Wontat was asked to look into the possibility of securing a professional historian who might continue work on the medical history of North Dakota called "Medical Milestones."

Election of officers was the last item of business. Dr. Borland was elected chairman; Dr. Toomey, vice-chairman, and Dr. Peters, secretary. The meeting was adjourned at 6 p. m.

The Interim Meeting of the Council was called to

order at 2 p.m. on December 9, 1961, at the Gardner Hotel in Fargo.

All councillors were present. Others present were Drs. E. H. Boerth, E. J. Larson, Amos Gilsdorf, Lee Christoferson, W. M. Buckingham, C. M. Lund, O. W. Johnson, O. A. Sedlak, Ralph Mahowald, Robert Nuessle, and Mr. Charles Johnson of the A.M.A., Mr. Mayo Christianson from Blue Cross, Mr. Daniel Buchanan, Mr. Lyle A. Limond and Mrs. Margaret Fremming.

Dr. Mahowald presented a program developed by the Emergency Medical Service Committee to implement medical self-help throughout North Dakota. It entails teaching individuals the basics of caring for themselves and their families in event of national disaster. The teaching program is to be handled initially by doctors of medicine. Dr. Mahowald asked that the presidents of the 10 district medical societies be asked to submit the name of a member who would be willing to work. The motion was made and carried that the North Dakota State Medical Association make available \$150 to this committee for implementation of its work. The council expressed appreciation of Dr. Mahowald's concise report.

A letter was read from Mr. W. R. Myhra of Fargo requesting that Mr. Lyle A. Limond accept the chairmanship and the responsibility of working with the members of the North Dakota State Medical Association in the cause of Radio-Free Europe. A motion was made and carried that Mr. Limond be urged to accept this chairmanship.

A letter was read from Dr. Albert Samuelson asking approval for formation of the North Dakota Psychiatric Association. The council approved.

Mr. Charles Johnson of the Field Services division of the American Medical Association was introduced. He discussed points of a suggested national legislative program for the North Dakota State Medical Association for 1962. The motion was made and carried that the council approve the suggestion, and that it be referred to Dr. O. W. Johnson, chairman of the Committee on Legislation.

Dr. Pederson advised that a scheduled meeting of the House of Delegates of the American Hospital Association might reverse its stand and pass a resolution to support the King-Anderson bill. The motion was made and carried that each councillor contact the board of trustees of hospitals in his area and urge it to send letters and telegrams of protest to the executive director of the American Hospital Association.

Mr. Mayo Christianson of the North Dakota Blue Cross presented a summary of the study underway on the use of hospital facilities in North Dakota. While the question of over-use of hospital facilities was primary in the initiation of this study, it also was felt that valuable information might be obtained to improve hospital administration and health service. Since the study has not been completed, Mr. Christianson had no information about definite trends being developed. The council suggested that members be asked to consult with him periodically. Drs. Borland and Christoferson were suggested as a committee to work with him.

Dr. Nuessle, chairman of the North Dakota Advisory Committee to Selective Service, addressed the council. He said that no national committee had been set up for guidance on policies and standards. In many instances, small towns in North Dakota have gone to great lengths in obtaining a physician for their community. Since there is only one doctor to 1,400 persons in the state, each physician is highly essential. It was suggested to Dr. Nuessle that he continue to make every effort to keep essential men in small towns and to work closely with

the councillors in each district. A motion was made and carried that a vote of confidence be given to him, stating that the council feels he is doing everything possible to make decisions in a fair, but not arbitrary manner, and that he has the confidence of the council.

Dr. Pederson, chairman of the Committee on Aging, presented a motion that each district's president appoint a 3-man committee on aging in his society to work closely with the state committee.

Dr. Amos, new State Health Officer for the State of North Dakota, was welcomed and introduced. He stated that some federal funds have been made available to the state for a visiting nurse service and a homemakers' service. He said there was more need for the visiting nurse service at this time. He suggested a pilot program, possibly in the First District area. He said this service could be administered through a voluntary local nursing board or a local health department, with the public health service assisting. The objectives of the program are: (1) to make home nursing services available to the chronically ill, (2) to reduce cost of hospitalization to chronically ill patients, (3) to alleviate hospital bed shortages, (4) to decrease need for more hospital beds, and (5) to educate patients to help themselves. A motion was made and carried approving a pilot study such as outlined by Dr. Amos.

A letter was read from the Medical Association of the State of Georgia concerning a resolution it had passed stating that the various county medical societies go on record stating that the American Medical Association represents their will and desire and that the present leadership of the American Medical Association enjoys the full confidence and support of the entire membership of the Medical Association of Georgia. This resolution was introduced and passed because of the numerous efforts by political opponents of the A.M.A. in recent months in the press and other media to discredit the A.M.A. by insinuating that it does not have the support of the majority of practicing physicians in the country. A motion was made and carried that the council pass an affirmative resolution endorsing the resolution from the State of Georgia and that a copy of the resolution be mailed to each district secretary to be read to the membership.

Dr. Peters made a motion, which was seconded and passed, that a letter of commendation be sent to the legal staffs of the American Medical Association's Chicago and Washington offices for their diligent work on the King-Anderson hearings.

Dr. Boerth informed the council it had been his privilege to present a check for \$250 on behalf of the North Dakota State Medical Association to the teacher of the student winner of the contest sponsored by the Governor's Committee for the Employment of the Handicapped. He said this gesture had been so well received that a similar presentation should be made in 1962. A motion was made and carried to that effect.

Mr. Limond presented a resolution passed by the North Central Medical Conference in Minneapolis on November 5, 1961, urging each member state to foster active participation in the American Medical Political Action Committee (AMPAC). The council approved the general idea of forming an AMPAC committee in North Dakota. Drs. Boerth and Johnson volunteered to take initial steps.

Mr. Albert Hartl, president of the Otter Tail Power Company of Fergus Falls, Minnesota, spoke at dinner.

The council reconvened at 8:20 p.m. Mr. Limond discussed the proposed budget for 1962 and advised that

the executive committee had examined 1961 expenditures. A motion was made and carried that the proposed 1962 budget be accepted.

Dr. Boerth reported on the reception given by the association for Dr. L. W. Larson in New York City following his election as president of the American Medical Association.

A report was made on the actions of the Committee on Medical Economics which had met earlier in the day.

The following resolution from the committee was read: "Dr. Keith Foster moved that the Public Welfare Board of North Dakota be notified that no fee schedule agreements will exist in regard to the several public assistance categories, as well as the fee schedule agreement for the Crippled Children's Services Program after ninety days from the date stipulated in the letter of notification, and that the council of the North Dakota State Medical Association be asked to concur in this motion."

Dr. Peters reviewed the meetings and correspondence with the Public Welfare Board, including the letter directed to the Attorney General by the Welfare Board asking if it was mandatory to negotiate with this association. Mr. Bergum's opinion stated "It is not mandatory that the Public Welfare Board negotiate with the Medical Association. However, if no agreement is reached with the Medical Association, we do not believe that fee schedules adopted for other types of assistance are binding upon the Medical Association unless specifically provided for in such an agreement, insofar as medical assistance to the aged is concerned. If agreement is not reached by negotiation, the Public Welfare Board must then pay as billed for such services rendered, providing the bill is reasonable."

A motion was made and carried that the council accept the motion as submitted by the Committee on Medical Economics and that notification be sent to the Public Welfare Board, as requested.

Dr. Boerth addressed the council and praised committee members for their work and good attendance at meetings. He reported he has visited the South Dakota State Medical Association and invited it to Bismarck in June 1962 for a joint meeting of the two associations. He suggested measures for the use of medical disciplinary committees.

Dr. Wontat said he had talked with a professional historian, Dr. Robinson of the University of North Dakota, an associate professor of history, and discussed the possibility of revision of "Medical Milestones." Dr. Robinson was interested in reviewing the material and may be free to work on it by late summer or early fall. Action on this matter was tabled until the spring council meeting.

A motion was made and carried that the council concur with the Executive Committee in the hiring of Mr. Daniel Buchanan as Director of Public Information and Education at \$5,100 a year.

A motion was made and carried that the council concur with the Executive Committee in retaining William Daner of Bismarck as legal counsel at a retainer fee of \$75 per month.

Dr. Wontat advised that he had checked into the personnel of the medical department at the University of North Dakota for possible members for the association. Only one physician was found eligible. Dr. Wontat will invite him to join. Dr. Pederson was requested to survey personnel at the State Hospital to see if the doctors are interested in joining.

Dr. Lund, speaking as the chairman of the Committee

on Cancer, discussed the actions of his committee. He had been requested to bring to the council a resolution made by his committee supporting the American Cancer Society's stand regarding smoking by young people. A motion was made and carried that the council endorse the work of voluntary health agencies in bringing an educational program on harmful effects of smoking to the attention of young people.

A motion was made and carried that the council approve the appointment of Mr. Lyle Limond as secretary of the North Dakota State Board of Medical Examiners. The council adjourned at 10:50 p.m.

The Executive Committee in late January 1962 approved a year's sponsorship of a weekly half hour newscast on 4 local television stations which will emphasize the free enterprise economic system. This is to be a cooperative venture involving the Greater North Dakota Association, the North Dakota Banker's Association, privately owned utilities, railroads, and possibly other companies in North Dakota, and the North Dakota State Medical Association. The cost to the association will be \$1,000. The total cost is to be \$16,000, with the Greater North Dakota Association furnishing the first \$5,000. The remaining \$11,000 will be made up by other participants.

V. G. BOBLAND, M.D., Chairman

Addendum:

REPORT OF NEGOTIATIONS WITH THE STATE WELFARE BOARD, APRIL 18, 1962

MR. CARLYLE D. ONSRUD, Executive Director
Public Welfare Board of North Dakota
Capitol Building
Bismarck, North Dakota

Dear Mr. Onsrud:

This is to inform you that the Council of the North Dakota State Medical Association met by a telephone conference on April 19, 1962, to consider the proposals of the Public Welfare Board, as adopted at its meeting of April 18, 1962, and subsequently modified by telephone conversations with Mr. Atkins on April 19, 1962. The council's acceptance of proposals submitted to it has, it is believed, finalized agreement between the State Medical Association and the Public Welfare Board as follows:

(1) The Medical Association recedes from its demand that the new fee schedule be applied retroactively on MAA accounts for a six-month period and agrees to accept payment of such accounts based on the OAA schedule superseded by this agreement. This action is based upon acceptance of the relative value fee schedule, proposed in the alternative, hereinafter set forth.

(2) The attorney for the Welfare Board and the attorney for the Medical Association will collaborate on a revision of the rules and regulations of the Public Welfare Board as they pertain to physicians and the treatment of welfare patients. The revised rules and regulations and future rules and regulations proposed by said attorneys will be submitted to the Welfare Board for approval and promulgation.

(3) The Public Welfare Board will employ a cost-of-living index mechanism to revise biannually the physicians' fee schedules covering medical service to welfare patients. The Board will initiate this practice in connection with the preparation of its 1963-1965 budget this year so as to reflect any increase in the cost of living since February 1960.

(4) Physicians' fees for services provided under the Crippled Children's Services program are excluded from this agreement, it being understood that as far as possible, the Crippled Children's Services will adopt a fee schedule comparable to the Public Assistance fee schedule, and that the participating physicians will be given the option to accept the CCS fee schedule on an individual basis, as has been the practice in the past.

(5) Because the patients being treated under the MAA program do not, at the present time, constitute a group separate and distinct from those treated under the OAA program, no separate medical fee schedule under the former is warranted. It is understood and agreed, however, that should legislation be enacted increasing the income limits under the MAA program or making any other changes that would result in a differentiation in the application of the MAA program as contrasted to OAA, the presentation by the North Dakota State Medical Association will be given serious consideration by the Public Welfare Board of North

Dakota, and a separate fee schedule will be warranted and considered by the Board at that time.

Until then the differences of opinion concerning fees are resolved by the adoption of the following relative value fee schedule to be used in connection with the several welfare programs, with the exception of Crippled Children's Services:

Medicine	\$2.50 per unit	Surgery	\$3.00 per unit
Pathology	1.00 per unit	X-Ray	5.00 per unit

It is further understood and agreed that the Public Welfare Board will accept adjustments or revisions in the relative value fee schedule, as the same may be adopted from time to time by the members of the North Dakota State Medical Association, including those adopted on March 3, 1962, it being understood that such adjustments will be in the relative value only and will not involve an over-all increase or decrease in the dollar value of the unit as outlined above.

The foregoing agreement is effective as of April 20, 1962.

Lyle A. Limond
Executive Secretary

The foregoing outline of the agreement formulated by the acceptance of the State Medical Association of certain proposals propounded by the State Welfare Board has been reviewed and found to correctly reflect said agreement as understood by the Public Welfare Board.

Carlyle D. Onsrud

The negotiating team for the North Dakota State Medical Association includes Drs. C. H. Peters, Bismarck; M. A. K. Lommen, Bismarck; O. V. Lindelow, Bismarck; and E. J. Larson, Jamestown.

REPORTS OF COUNCILLORS

First District

The First District Medical Society held 8 meetings during the fiscal year from March 1961 through February 1962 in the town hall of the Gardner Hotel in Fargo on the fourth Tuesday of each month.

On March 28, 1961, Dr. Edwin P. Wenz was elected to membership. Dr. Maxwell Lockie of Buffalo, New York, was guest speaker. His topic was "Cout."

The April 25th meeting considered immunization for polio. It was estimated that at least two-fifths of the people in Fargo are not immunized. Doctors were urged to interest more patients in immunizations. The meeting of the North Dakota State Medical Association to be held in Fargo in May was discussed and committees were appointed. There was discussion of the forthcoming meeting of the House of Delegates in May. A claims committee was appointed: Drs. Oliver Sedlak, Arthur Burt and M. H. Poindexter.

At the meeting on September 26, there was discussion about formation of a planned parenthood program to be carried out by the Public Health Department. The society went on record as approving such a program. The society was addressed by Dr. Edwin Boerth, president of the North Dakota State Medical Association. He discussed actions of the recent special meeting of the House of Delegates. Dr. James Mahoney of Devils Lake, chairman of the State Public Relations Committee, gave an interesting talk on programs of his committee.

The meeting on October 20, 1961 featured the annual Long-Darrow lectureship. Dr. Maxwell M. Wintrobe of the University of Utah Medical School spoke on "the Diagnosis and Treatment of Anemia."

The meeting on November 28 considered several business matters. Committee chairmen made reports. The scientific portion was conducted by Dr. Charles Neumeister of Minneapolis, who spoke on "Problems in the Care of Patients with Carcinoma of the Lower Colon and Rectum."

The annual meeting was held on December 12. The following officers were elected for the coming year: president, Dr. C. M. Hunter; vice-president, Dr. Frank M. Melton; and secretary-treasurer, Dr. Richard J. Zauner. Named as delegates to the state meeting were: Drs. Burt, Hall, Melton, Houghton, Bacheller and Norum. Alter-

nates are Drs. Schneider, Jachning, Wold, Christoferson, Murray and Thompson.

The board of censors consists of Drs. L. G. Pray, Ralph Weible, and George Ivers.

A program on estate planning was presented by the Northwestern National Bank, Minneapolis.

Dr. C. M. Hunter presided at the first meeting of the new year on January 30, 1962. Drs. Kohlmeier, Nicholson, Owens, Kelly, and Beithon were elected unanimously to membership. Dr. Amos of the North Dakota Public Health Department spoke. Dr. Ralph Mahowald of Grand Forks, chairman of the Emergency Medical Service Committee, gave a stimulating talk on the program being developed by his committee to teach lay people the rudimentary aspects of self-help during periods of emergency.

At the February 27 meeting, Dr. Thomas Hamilton was voted into membership. Dr. Douglas Lindsay reported on the recent action of the Civil Defense Committee. It was decided that the society should embark on a publicity campaign and insert advertisements in the local newspapers every two weeks. This is to be carried out under direction of the Public Relations Committee. The society went on record of full support for the American Medical Political Action Committee (AMPAC).

Membership of the district is as follows: active members, 95; retired members, 1; honorary members, 2; limited members, 10; in-service members, 0; new members added during the year, 7; members who have left the state, Dr. Ralph Tarnasky, Fargo, and Dr. Daniel Levson, Fairmont; deceased members, Dr. Budd Corbus; and nonmembers residing in the area, 0.

V. G. BORLAND, M.D., Comcillor

Second District

The Devils Lake District Medical Society held 10 meetings during the past year, including a special one. Attendance was excellent. New members have joined and there have been interest and discussion concerning present problems, political and otherwise. Officers for the present year, elected at the January meeting, include Dr. Elmer Schwinghamer, New Rockford, president; Dr. D. G. McIntyre, Rugby, vice-president; and Dr. L. F. Pine, secretary-treasurer. Delegates are Drs. Hilts and Seibel. Alternate delegates are Drs. O. W. Johnson and R. D. McBane.

The following speakers and programs were included at meetings.

April 4: Dr. Schmidhofer of Jamestown spoke on "Psychiatric Problems."

March 1: Most of this meeting was taken up with the Central Professional Claims Committee of the North Dakota Physicians and Hospital Service. Many interesting points were brought out. Mr. Buchanan, Director of Public Relations, introduced a resolution for endorsement by our society regarding the King-Anderson bill. The resolution was adopted, but not unanimously.

February 1: Dr. Wenz of Fargo spoke on "Treatment of Fractures About the Ankle Joint." Dr. Cuadrado of San Haven transferred from the Northwest District to the Devils Lake District. Dr. Neuenschwander of Rolla was admitted as a member.

February 22: Dr. Richard DeWall, cardiac surgeon from the University of Minnesota, attended this extra meeting.

January 11: State President Boerth gave an excellent presentation of the current problems of the state society. The comcillor from the Second District gave a full re-

port on the Interim Meeting of the Council, and said that members of the society would be informed as to what is going on at the state level. Mr. Lyle Limond and Mr. Dan Buchanan attended.

December 7: Dr. Towarnicky was admitted to the society. The program consisted of a film by the Cancer Society. Dr. Veenbaas, pathologist from Trinity Hospital, Minot, spoke on "Pathology as Seen in General Practice."

November 2: The scheduled speaker was unable to appear. Current problems, local and political, were discussed.

October 5: Guest speaker was Dr. Donald Campbell of the Mayo Clinic, who gave an excellent paper on "Some Aspects of Hematology." It was decided not to do anything about the Diabetic Drive this year. The AAPS essay contest for high school students was discussed. It was voted to go on record as approving, and that we contact the Devils Lake District Medical Auxiliary to sponsor it. We will provide financial support, as usual.

September 14: The program was presented by Dr. John V. Sessums of the Dakota Clinic. He gave an informative discussion on "The Problems of the Neonate," followed by a question period. Application for membership by Dr. Joseph L. Nosal was approved.

May 25: This was a special meeting following the state meeting. Reports were given by the comcillor and delegates.

All in all, it has been a very interesting year.

G. W. TOOMEY, M.D. Comcillor

Third District

Since the last report, this district society has met on the third Thursday of each month except May, June, July, and August, and has held one special meeting.

On March 16, 1961, in Grand Forks, Dr. Gerald Cooper of the Communicable Disease Center in Atlanta, Georgia, discussed "Infectious Hepatitis." Routine business was transacted and \$100 was voted to support the High School Science Fair.

On April 20 Dr. B. M. Black of the Mayo Clinic discussed: "Carcinoma of the Thyroid Gland." Blue Shield and legislative matters were discussed.

On September 21 in Grafton, Dr. Thorlaakson of the Winnipeg Clinic discussed "Office Proctology." Routine business matters were transacted and Drs. Ione Dzinbur of Northwood, Curtis Sande of Larimore, and George Wilson of Grand Forks were elected to membership. Dr. C. J. Glaspel of Grafton discussed the work and some of the problems of the secretary of the State Board of Medical Examiners. A sum of \$100 was voted to support a Diabetes Detection Drive.

On October 19 in Grand Forks, Dr. J. Roy Amos, North Dakota State Health Officer, discussed State Health Department functions. An American Cancer Society film, "Life Story," was shown and approved for public showing in this area. M.A.A. and State Welfare Board problems were discussed.

In October we held a special joint meeting with the local Bar Association at which a film on medicolegal matters and courtroom procedures was shown. A general discussion of mutual problems followed.

On November 16, in Grand Forks, Dr. Ernst Morch of Chicago discussed "Respiratory Physiology" and demonstrated the Morch respirator. Routine business was transacted.

On December 21, in Grand Forks, Doctor E. A. Hamz gave an illustrated "Report from Europe" with movies and slides. General discussion followed. Routine business was transacted, and Dr. John Cooselaw of the University

of North Dakota Medical School was elected to membership.

On January 18, 1962, in Grand Forks, Dr. Paul Quie of the Pediatric Department of the University of Minnesota discussed "Staphylococcal Infections." The membership of Dr. Victor Szyrnski was transferred from the Sixth District to the Third District. Blue Shield and legislative matters were discussed.

The following officers were elected: president, Dr. Wallace W. Nelson; first vice-president, Dr. John H. Graham; second vice-president, Dr. Harold Piltingsrud; secretary-treasurer, Dr. Harold Evans. The board of censors includes Drs. R. E. Leigh, E. L. Grinnell, and T. H. Harwood. Delegates to the house of delegates are Drs. Robert Painter, R. E. Mahowald, R. H. Leigh, John A. Sandmeyer, and G. L. Countryman. Alternates are Drs. W. C. Dailey, B. J. Clayburgh, William P. Keig, Charles B. Porter, and Robert H. DeLano.

On February 15, in Grand Forks, Dr. C. D. Creevy, professor of urology at the University of Minnesota Medical School, discussed "Organic and Functional Obstructive Lesions in the Urinary Tract in Children." Routine business matters were transacted.

The society has 81 members and 4 honorary members. Two honorary members, Drs. R. D. Campbell and F. W. Deason, died during the past year. One member left the state and another is in military service.

The Society is in good financial condition.

P. H. WOUTAT, M.D., Councillor

Fourth District

This District had a successful and busy year. The following new members were admitted to the society: Drs. William LaRochelle, Stanley; Fred Veenbaas, Minot; Kenneth Morrow, Minot; Justo Mari, Bottineau; B. Jayapathy, Minot; Norman Lloyd, Minot; Kermit Leonard, Garrison; A. M. Cameron, Minot; W. B. Eilers, Minot; and C. Robert Miller, Bottineau.

The following members transferred to other states: Drs. Norman Lloyd, Minot; G. S. Seifert, Minot; Otho Simms, Minot; and M. J. Towarnicky, Fessenden.

At the close of 1961, membership numbered 72, of which 2 were honorary and 70 active.

On September 28, 1961, Dr. Thomas Chin, Chief, Virus Laboratory, Communicable Disease Center, USPHS, Kansas City, Kansas, spoke on "Factors of Encephalitis Epidemic in North Dakota." On October 26, 1961, Dr. R. Hosie of Regina, Saskatchewan, Canada, spoke on the threatened socialized medical program in Saskatchewan, and Dr. Robert Soper of the Department of Surgery, University Hospital, Iowa City, Iowa, spoke on experiences in England with the socialized medicine program. At the meeting on January 25, 1962, Dr. Lloyd Sherman presented a paper entitled "Common Anorectal Problems and Cancer of the Anus and Rectum." On February 22, 1962, Dr. Walter Wasdahl, Department of Pathology, University of North Dakota, addressed the group on "Medicine and Pathology as Encountered in Africa."

F. D. NAEGELI, M.D., Councillor

Fifth District

The Shyenne Valley Medical Society held 5 dinner meetings during the fiscal year from March 1961 through February 1962. The first meeting was held March 27, when the Cancer Caravan furnished the scientific program. Speakers included Drs. A. Sullivan of the University of Minnesota, Phil Woutat of Grand Forks, Art

Burt of Fargo, John LeMar of Fargo, and John Gillam of Fargo.

On April 19, Dean Harwood of the University of North Dakota School of Medicine was our dinner guest. He discussed the medical school.

The next meeting was held May 17, when Dr. W. E. Cornatzer of the School of Medicine at the University of North Dakota discussed laboratory procedures and their significance and value.

November 15, 1961, Dr. John Magness of Fargo spoke on "Diseases of the Thyroid," with emphasis on differential diagnosis and diagnostic procedures.

A dinner and scientific program was held on January 17, 1962, at which time the following were elected: president, Dr. G. Christianson; vice-president, Dr. Warren R. Jensen; secretary-treasurer, Dr. C. J. Klein; delegate, Dr. Clayton E. Jensen, and alternate, Dr. N. A. Macdonald.

Dr. W. A. Kelly, an orthopedic surgeon of Fargo, lectured on "Fractures of the Lower Extremities." This was followed by a review of x-ray films of orthopedic problems.

With the transfer of Dr. James Hoyne of Oakes to Tioga, the Fifth District now has a total active membership of 8 and 1 retired member.

We continue to have a "quack" practicing medicine in our district. This man gives injections and dispenses medicine. To date, it seems that nothing can be done to curb his activities.

G. CHRISTIANSON, M.D., Councillor

Sixth District

Since the last report to the House of Delegates the Sixth District has had the following meetings: April 26, 1961: The scientific speaker was Dr. Lee Christoferson of Fargo, speaking on neurological injuries. In addition to 52 members in attendance, Mr. Cohn, science editor of the Minneapolis Tribune, was our guest. Dr. Victor Szyrnski, Dr. James Moses, Dr. Demetrios Daniolos, and Dr. Cecil Baker were voted into full membership. Dr. Arnold Kahins of Washburn was unanimously elected to represent the society to the Blue Cross board of directors.

With the approval of the society, the president appointed a Review Committee, purpose of which is to make its services available for the examination of claims submitted by Blue Shield-Blue Cross, commercial insurance carriers, and state and federal agencies when disputes arise between these organizations and patients or physicians. The Review Committee is to be on a rapid rotation basis, to give all members experience in this field. A motion was made, seconded, and passed to instruct the delegates to the state convention that the Sixth District Society moves the adoption of a Review Committee in each district.

The Glaucoma Detection Clinic, to be sponsored by the ophthalmologists in Bismarck in June, was approved.

September 28: There were 46 members in attendance. Our speaker was Dr. William E. Cornatzer of Grand Forks, who discussed body cholesterol.

Dr. Gaebe of New Salem was recognized, after having retired from 50 years of medical practice. Dr. Amos of the State Health Department, and new director of the Public Health Department, was introduced. Dr. Albert Sammelson was welcomed upon his return after training in psychiatry at the Menninger Clinic. He is now with the State Children's Psychiatric Clinic in Bismarck.

Dr. Ralph Dunnigan had been chairman of the Review Committee. Dr. Froeschle, president of the society,

appointed Dr. Moses to replace him. The other members are: Drs. Girard, Tudor, Baker, and Henderson.

The secretary-treasurer had made a donation of \$25 from the society to the Dakota Boys Ranch in honor of the late Dr. C. W. Schoregge, and a \$25 donation to the North Dakota State University medical loan fund in honor of the late Dr. R. H. Waldschmidt.

The following officers were elected: Dr. Paul Johnson, was elected president; Dr. M. A. K. Lommen, vice-president, and Dr. C. R. Montz, secretary-treasurer. Dr. Phillip Dahl was named delegate, his term ending in 1964. Dr. Percy Owens was named to the Board of Censors, his term ending in 1964. Drs. Joseph Cleary and M. J. E. Johnson were named to the board of directors of the North Dakota Physicians Service, their terms ending in 1964.

February 6, 1962: Our last regular meeting had 55 members in attendance. Dr. Paul Johnson, president, presided. The scientific speaker was Dr. A. F. Samuelson of our own group, psychiatrist at the North Dakota State Child Guidance Center in Bismarck.

Dr. Phillip Dahl, a member of the Legislative Committee, reported on his attendance at the public relations meeting held by the American Medical Association in Chicago in January, 1961, and on the meeting to be called by Dr. O. W. Johnson, chairman of the State Committee on Legislation, to be held in Fargo on February 17, 1962.

The report from the Review Committee, established to go over disputes on claims, was given by Dr. Moses. He stated there was little activity. The same committee was reappointed to stay in office for one year. Apparently there had been little action from commercial carriers, Blue Shield or Blue Cross, or federal and state agencies in seeking the help of this committee.

Dr. Robert Olson and Dr. Hans Fischer were unanimously elected to membership.

A motion was passed that the Executive Board be empowered to place ads in local newspapers without restrictions. It was felt it would help public relations between the physician and the laymen within the area of the society.

A motion was made and passed that the Sixth District go on record to oppose the adoption of the Professional Service Index, but that it favors full cooperation with the National Blue Shield program by utilizing the present North Dakota relative value schedule with an appropriate conversion factor.

The district has 85 active members, 1 retired member, and 4 honorary members. We gained 6 new members. Drs. C. W. Schoregge, R. H. Waldschmidt, and A. M. Fisher died during the year.

C. H. PETERS, M.D., Councillor

Seventh District

During the past year, 9 dinner meetings were held. The first meeting was March 30, 1961, with 13 physicians and 2 guests in attendance. The County Society again sponsored an essay contest in the local schools and awarded prizes of \$40. The program was presented by Dr. Ed Ohmstead of the University of North Dakota. He spoke on "Treatment of Refractory Heart Failure."

The meeting April 27 had 21 doctors and 2 guests in attendance. The program was presented by Drs. Burt and Sedlak of Blue Shield, and Don Eagles, executive secretary of Blue Shield. The problems inherent in administering Blue Shield were discussed, together with other practical ramifications. Dr. E. J. Larson reported

the action of the Medical Economics Committee in its negotiations with the Public Welfare Board.

At the May 25 meeting there were 14 doctors and 4 guests. A Medical Reviews Committee for Blue Cross-Blue Shield and other insurance committees was appointed. Our delegates to the state association meeting gave a report of the proceedings of the House of Delegates. Dr. Larson repeated the report of the Medical Economics Committee. A film, "Blood Fractions in Clinical Medicine," was shown.

The meeting October 10 had 21 doctors and 5 guests in attendance. This was the official visit of the president of the society, Dr. Ed Boerth. He was accompanied by Dr. James Mahoney, chairman of the Public Relations Committee of the State Association; Lyle Limond, executive secretary, and Dan Buchanan, director of public relations. Dr. Boerth commented on the special session of the House of Delegates held September 24 and made pertinent comments on association policies, philosophies and goals. Dr. Mahoney gave a brief talk on "inner-physician relations," and Dan Buchanan discussed the relations of the association with the press and other communications media.

The November 2 meeting had 21 physicians in attendance. It was sponsored by Superintendent Ernst Schmdhofer of the State Hospital, with the social hour and dinner at the State Hospital. He introduced the speaker of the evening, Dr. Francis J. Braceland, a Psychiatrist in charge of the Institute of Living at Hartford, Connecticut. Dr. Braceland spoke on "Anxiety and Depression in General Practice."

The next meeting was December 7, with 27 members and 4 guests in attendance. There was discussion of instituting a public relations program, and \$200 was set aside for financing one. Dr. Robert Ivers of Fargo spoke on "Headaches."

The January 25 meeting had 19 physicians and 3 guests in attendance. Dr. Pederson gave a report on the council meeting in December. The program consisted of films, one of the A.M.A. convention, and the other on Malignant Polyposis of the Colon.

Dr. C. W. Hogan, Jamestown, was elected president; Dr. Donald Schmidt, Gackle, vice-president; and Dr. R. D. Nierling, Jamestown, secretary-treasurer. Drs. John Elsworth and John Van der Linde, Jamestown, were named delegates. Drs. D. M. Clement and A. F. DuMals, Jamestown, were named alternates.

The next meeting was February 22, with 21 members and 5 guests in attendance. The legislative committee was appointed: Drs. J. N. Elsworth, Clarence Martin, Dayton Burkholder, John Beall and John Swenson. Dr. Clarence Martin of Medina spoke on "Hypnosis." This paper was discussed by Dr. Rioux. A discussion period and demonstration followed.

The March 22 meeting had 19 physicians and 3 guests in attendance, including Dr. Boerth and Lyle Limond. There was discussion about a podiatrist practicing in town and performing surgery and requesting x-rays from medical doctors. The society decided that any request by a podiatrist for x-rays should be denied unless the patient is thoroughly examined by the physician himself. Dr. Boerth commented on the Kerr-Mills law and the voiding of the welfare schedule April 1. The reports of the legislative and public relations committees were made, and an additional \$250 was appropriated to carry on a more militant public relations program. It was decided that the Annis film be televised over Channel 4. It was moved that resolutions be sent to the legislators in Washington reporting the feelings of the society on

the King-Anderson legislation. The Annis film, "Where Is Medicine Going," concluded the meeting.

The Seventh District has been active in public relations efforts with newspaper ads, radio spots and TV sponsorship of the Annis film.

There are 36 active members in the society. New members admitted during the past year are Drs. T. Evangelista, Robert Nolan, A. F. DuMais, and Dayton Burkholder. Dr. Lengyel transferred to New York.

T. E. PEDERSON, M.D., Councillor

Eighth District

The Eighth District Society held 5 meetings during 1961.

On May 17, a meeting in the Plainsman Hotel honored Dr. C. M. Lund, immediate past president of the association. Appreciation of his efforts on our behalf was expressed by Dr. H. Charles Walker, Jr. A token gift was presented. A paper was presented by Mr. Warren Duntley, executive director of the North Dakota Heart Association, on "Stroke Rehabilitation." A film was shown. A business meeting followed. Dr. James Hoyme of Tioga was accepted as a member.

On October 4, the society met in regular session at the Plainsman Hotel. Dr. T. H. Harwood, Dean of the School of Medicine at the University of North Dakota, addressed the group on the future of medical education. A discussion period followed.

Brief special meetings were held on January 18 and March 23.

On January 24, 1962, the regular annual meeting was called to order by Dr. Walker, Jr., president. Reports were submitted by the councillor regarding the December council meeting. Action was taken as requested, approving the policies of the A.M.A. and action regarding AMPAC.

A report of the Blue Shield board committee was given.

The following officers were elected: president, Dr. Milton Berg, Tioga; vice-president, Dr. H. Inness-Brown; secretary-treasurer, Dr. Charles R. Petty. Dr. Dean Strinden was elected delegate and Dr. Thomas Sussex, alternate. Dr. Donald Skjei was named to the Blue Shield board. The present Board of Censors was retained.

The Eighth District has 17 active members. There are 3 non-members practicing in the district. We gained 1 new member and lost 2 this past year.

JOSEPH D. CRAVEN, M.D., Councillor

Ninth District

We started our year on a sad note with the death of Dr. C. R. Dunkart, a long-time physician in Richardton and Dickinson. Our meetings never will be the same without "Chris." He will be missed greatly by his associates and friends.

Our June meeting consisted of the now annual gathering in Mott, where Dr. and Mrs. Hankins continued their fine record of hospitality.

Most of the October 14 meeting was devoted to matters on a social economic vein and on the state of public relations in our area.

At the December meeting the following officers were elected: president, Dr. Henry Slominski; vice-president, Dr. A. R. Gilsdorf; secretary-treasurer, Dr. W. C. Hancwald; councillors, Drs. K. G. Foster, Robert Thom, and R. F. Rasmuch; delegates, Drs. Norman B. Ordahl and W. C. Hancwald; alternates, Drs. Robert Hankins and Robert Gilliland.

Dr. Roger Berg gave a fascinating presentation on cineangiocardiology.

The evening was our annual Christmas party.

Since the first of the year we have instituted a panel series of programs on the local station KDIX called "T.V.-M.D." We appeared in rotation to attempt to cover points of medical, public health and economic importance. This apparently has been well received by our patients.

To improve public relations, we had a meeting in March with local attorneys, who were our guests at cocktails and dinner. Two medical-legal films were shown as points of departure for a discussion on problems inherent in both professions.

The April meeting is the official visit of Dr. Ed Boerth, state president.

K. G. FOSTER, M.D., Councillor

Tenth District

The Tenth District society held 4 scientific and business meetings in 1961. Many members have remained active during the year, with talks with both the general public and with legislators concerning state and national legislation problems. We also have been active in informing the public about the King-Anderson bill and our already-functioning Kerr-Mills bill.

Most members have been active in attending their committee meetings, and in functioning in their own locale to carry out recommendations of the state association.

We have 12 active members. Dr. Karl Oja has been accepted from the Sixth District. There are no non-members residing and practicing in our district.

Officers elected to serve in 1962-63 are as follows: president, Dr. Russell Odegard, Hatton; vice-president, Dr. Lars Vistnes, Cooperstown; secretary-treasurer, Dr. R. W. McLean, Hillsboro. Named to the Board of Censors were Dr. Kenneth Wakefield, Cooperstown (three years); Dr. R. C. Little, Mayville (two years); and Dr. H. A. LaFleur, Mayville (one year). Dr. James Little, Mayville, was named delegate and Dr. Kenneth Wakefield, Cooperstown, alternate.

R. W. McLEAN, M.D., Councillor

REPORTS OF STANDING COMMITTEES

Committee on Medical Education

At an April 30 meeting at Fargo there was discussion of the giving of equal credit on loans from the medical school to men who return to the state for internships and residencies and to those who return to practice in communities where a doctor is needed. The opinion was that the legislative committee should consider the feasibility of having the law amended to give equal credit.

Dean Harwood discussed problems of the medical school and the need for more applications from the state.

There was discussion of the Rehabilitation Center.

An October 29 meeting was attended by Dr. H. Milton Berg, chairman, and Drs. Swenson, Kermott, Ulmer, Keller, Gilsdorf, and Harwood. Mr. Buelman was present.

Dr. Berg read the report of the Reference Committee on Medical Education which had been presented at the May meeting of the House of Delegates by Dr. Mahoney. The reference committee at that time approved the Committee on Medical Education's recommendation that students who return to North Dakota for internship be given credit on their student loans. It gave approval of

the intention of the medical education committee in protesting that foreign medical graduates are being treated more abruptly than diplomacy might find wise. It gave approbation and support to the attitude of the Committee on Medical Education in its desiring comparable and competitive salary and fringe benefits for faculty and staff at the medical school in relation to medical schools across the nation. Dr. Berg noted that the report of the reference committee had been adopted by the House of Delegates.

The meeting then was turned over to Dean Harwood of the medical school. The dean told the committee that, effective last July 1, dental students had become eligible for Medical Center Loan Act loans. He also pointed out that it is now possible for medical students to complete their internships and residencies before note payments fall due. He said it would take some years to ascertain whether the "forgiveness clause" will be successful in bringing medical graduates back to North Dakota.

A motion was passed that the "forgiveness clause" on loans be extended to residents.

Dr. Harwood reported that the faculty at the medical school feel well-paid, and that salaries are above the national norm. He did stress, however, the need for adequate fringe benefits, and said the Board of Higher Education had been reminded again and again that the medical school in North Dakota is at a disadvantage because of its incomplete and inadequate retirement plan.

Dean Harwood also explained the North Dakota teachers' retirement plan, Teachers' Insurance Annuity Association, and a program called "C.R.E.F."

It was moved, seconded and passed that everything possible be done to increase salaries and fringe benefits for medical school faculty members to meet the competition of other medical schools.

Dean Harwood reported that a team representing the A.M.A. Council on Accreditation of Medical Schools would inspect his school the week of November 5-11. He said that all recommendations made by the A.M.A. during its previous inspection in 1953 had been implemented, and that no difficulty was anticipated with regard to the 1961 visit.

The Dean also stated that:

1. Of all the students graduated from UND Medical School in the last nine years, only 1 failed to complete his medical education. The reason was health, not insufficient preparation.

2. The Medical School will have a Hill (Cancer Research) professor starting in January 1962 at a salary of \$15,000 per year for five years.

3. Deans of medical schools were polled recently and 85% said they would accept federal financial aid with no qualms.

4. It would be some 8 to 10 years before the private medical school in St. Paul, Minnesota, would be in operation.

5. The University of Minnesota Medical School is now accepting one student from each third of the UND medical school graduating class, and he trusts that good relations with Minnesota will improve and be enlarged.

6. UND's Medical School will participate in a program called Medical Education for National Defense (MIEND).

7. One of the continuing problems of the medical school is the finding of better qualified applicants. Of 97 applications received this year, 44 were from North

Dakota students. He also discussed the problem of graduate students in non-medical fields receiving stipends annually of \$1,800 to \$2,500, while medical students receive nothing.

8. He is pleased with the growth and quality of the UND Medical Graduate School.

9. His school is cooperating with other training centers throughout the state in the field of medical technology.

10. He would like to help develop a postgraduate education program for doctors in small towns, preferably with a traveling consultant. This program could help rural doctors "keep in touch."

11. He is enjoying good inter-departmental rapport.

12. The school is working on the problem of doctors for small towns.

13. There are several internal problems at UND relative to academic areas.

The committee discussed A.M.E.F. and contributions by alumni and friends to medical schools throughout the country.

The committee decided to meet on the Saturday before the annual meeting of the House of Delegates on June 2, 1962

II. MILTON BERG, M.D., Chairman

Committee on Neurology and Medical History

*So live, that when thy summons comes to join
The innumerable caravan that moves
To the pale realms of shade, where each shall take
His chamber in the silent halls of death,
Thou go not, like the quarry, slave at night,
Scourged to his dungeon, but, sustained and soothed
By an unfaltering trust, approach thy grave
Like one who wraps the drapery of his couch
About him, and lies down to pleasant dreams.*

WILLIAM CULLEN BRYANT

C. R. DUKART, M.D.

Dr. Christopher R. Dukart, a Dickinson physician since 1948, died in his home May 4, 1961. He was 55 years old.

Dr. Dukart was born in Stark county on February 18, 1906, and was raised in the Dickinson community, attending St. Joseph's school. He attended Assumption Abbey at Richardton and was graduated from St. Mary's Catholic College, Winona, Minnesota, where he took pre-medical training.

In 1932 he was graduated from Creighton University School of Medicine, Omaha, Nebraska. Following his internship at St. John's Hospital, Fargo, he opened a practice at Hankinson. He moved to Richardton in 1934. He operated his own hospital until 1948, when he came to Dickinson to be associated with the Dickinson Clinic.

He was a member and a past president of St. Joseph's Hospital staff, a member of the National Geriatrics Society, in which he took an active part, a member of the Dickinson Elks, the Knights of Columbus (fourth degree), the Dickinson Lions Club, and a past president of the Richardton Lions Club.

He married Grace Blum on July 17, 1935. She survives him, along with three sons and a daughter.

R. D. CAMPBELL, M.D.

Dr. Robert Donald Campbell, pioneer Grand Forks physician and surgeon, died in a Grand Forks hospital June 12, 1961, at the age of 94.

Born in Erin Village, Ontario, Canada, January 8, 1867, the veteran physician's medical and military career spanned two continents and numerous countries. He was

graduated from the University of Manitoba Medical School, Winnipeg, in 1893, and was licensed to practice medicine in North Dakota in July 1894.

Dr. Campbell was a bugler with Company F, Winnipeg Rifles, in the second Riel rebellion and later served as a U.S. Army medical officer in World War I.

Dr. Campbell was guest of honor in Winnipeg in October 1958 as the sole living survivor of the first battle fought by the Royal Winnipeg Rifles in 1885.

For many years he was a director and chairman of the board of the First National Bank, which he helped organize in 1933 as a charter director. When he resigned the bank's chairmanship in January 1958, he was named honorary board chairman, a post he held until his death.

The bank established the Robert D. Campbell Foundation at the University of North Dakota in his honor in 1955. Dr. and Mrs. Campbell made gifts to the foundation in excess of \$165,000.

He was the first commander of the Grand Forks post of the American Legion, served as secretary to the North Dakota State Medical Association from 1897 to 1900, and was elected president in 1906. He became a member of the 50-Year Club of the association in 1943 and an honorary member in 1949.

He was preceded in death by Mrs. Campbell, who died in 1959 at the age of 88. They had been married 62 years. Their only child, a son, died in infancy.

C. W. SCHOREGGE, M.D.

Dr. Charles W. Schoregge, a Bismarck surgeon for 45 years, died unexpectedly at his home November 11, 1961. He had suffered from a heart condition for many years.

Born at Sleepy Eye, Minnesota, May 21, 1889, he was the son of Charles H. and Ida (Behnke) Schoregge. He received his primary education at New Ulm, Minnesota, and was graduated from high school there in 1907. When he was graduated from the University of Michigan at Ann Arbor in 1911, he was the youngest man ever to receive a medical degree there. He interned at Deaconess Hospital in Minneapolis and began his practice at Henderson, Minnesota, prior to joining the Quain and Ramstad Clinic in Bismarck. In 1925 he did postgraduate work at the University of Vienna. He became a partner in the clinic in 1934 and later, chairman of the board. In 1937 he was admitted as a diplomate in surgical specialties to the American Board of Surgery. He was a Fellow of the American College of Surgeons and of the International College of Surgeons.

Dr. Schoregge was active in the practice of medicine from the time he joined the Quain and Ramstad Clinic in 1916 until the time of his death. Although he had retired from active practice he continued to receive patients. He held membership in the Bismarck Masonic Lodge and the Scottish Rite bodies. He had served as president of the North Dakota Board of Medical Examiners, was chairman of the North Dakota Merit Council, and served as medical advisor to the North Dakota Workmen's Compensation Bureau. He was past president of the Sixth District Medical Society and became an honorary member of the medical association in 1961.

He is survived by his wife, the former Helen L. Bosel, whom he married in 1916, and two sons.

R. H. WALDSCHMIDT, M.D.

Dr. Reuben H. Waldschmidt, veteran surgeon and partner in the Quain and Ramstad Clinic, Bismarck, died in a Bismarck hospital on November 24, 1961, at the age of 67.

He was born on March 8, 1894, at Fond du Lac,

Wisconsin. After receiving his elementary school and high school education there, he attended Wartburg College and received his B.A. degree from Augustana College, Rock Island, Ill., in 1918. He served as a second lieutenant with a field artillery unit in World War I, and after the war enrolled at the University of Minnesota. He received his B.S. degree there in 1920 and his doctor of medicine degree in 1921.

Dr. Waldschmidt served his internship at Veterans Hospital in Minneapolis before coming to Bismarck in 1922, serving his preceptorship in surgery at the Bismarck Hospital. He joined the Quain and Ramstad Clinic staff the following year as a physician and surgeon. He became chairman of the clinic partnership on January 1, 1955. He resigned his partnership and as chairman on December 31, 1960, although he continued to practice medicine and surgery and maintained an office at the clinic.

He was a member of the Scottish Rite, Sojourners, and American Legion, and during his professional career he served on the North Dakota Board of Regents of the American College of Surgeons. He was a past president of the Sixth District Medical Society, president of the North Dakota State Medical Association, 1956-57, a governor of the American College of Surgeons, chairman of the board of examiners of the American College of Surgeons, and author of several medical articles.

In 1937 Dr. Waldschmidt was listed by WHO'S WHO among outstanding young American men. He was a great traveler, and with his wife, the former Margaret Huebner, journeyed extensively around the world.

He is survived by his wife, a daughter and a son.

B. C. CORBUS, M.D.

Dr. Budd C. Corbus, a specialist in urological surgery in Fargo since 1947, died December 4, 1961, in a Fargo hospital where had been hospitalized for some time. He was 54 years old.

He was born April 1, 1907, in Chicago, where he attended elementary school. He was graduated from the University of Wisconsin, the Harvard Medical School, and the University of Illinois.

He served in the U.S. Navy Medical Corps during World War II, and practiced medicine with his father in Evanston, Illinois, before locating in Fargo.

He was a member of Gethsemane Cathedral, the Elks, American Legion, York Rite, International College of Surgeons, American Urological Society, Northwestern Medical Association, and the Manitoba-North Dakota Urological Association.

He is survived by his wife, the former Roanne Longyear, whom he married in 1945, and three daughters.

F. W. DEASON, M.D.

Dr. Frank W. Deason, 74, well-known Grafton physician and Walsh County coroner, died unexpectedly at his home on January 25, 1962.

He was born in Grafton on September 27, 1887, the son of the late Mr. and Mrs. Christopher Deason. He was graduated from the Grafton High School in 1905. While a student he worked in a drug store and became a registered pharmacist at the age of 16.

He attended Northwestern University Medical School in Chicago and was graduated in 1910. He immediately began the practice of his profession at St. Thomas, where he remained until 1920, when he moved to Grafton, although still maintaining an office at St. Thomas.

He was on the original medical staff responsible for

the establishment of the Grafton Deaconess Hospital. He was named superintendent of the Grafton State School in 1938 and served in that capacity for 18 months. He also served 2 terms as mayor of Grafton. In 1955 he was named Walsh County coroner, a position he continued to hold until his death.

Dr. Deason was a long-time member of the North Dakota State Medical Association, and in 1960 was awarded a certificate of distinction for 50 years of practice in the state. That same year he was awarded a golden reunion certificate by the Northwestern University Alumni Association. He was active in Masonic affairs, a member of Temple Lodge No. 30, A.F. & A.M. at St. Thomas, and of Creseent Lodge No. 11, A.F. & A.M. at Grafton. He was a member of the Grafton chapter, Royal Arch Masons, St. Omer Commandery.

He is survived by a son.

A. M. FISHER, M.D.

Dr. Albert M. Fisher, 86, former superintendent of the North Dakota State Hospital, died unexpectedly at his home in Bismarck on February 4, 1962. He had been in failing health for several years.

He was born at Uniontown, Pennsylvania, on November 22, 1875, son of George and Martha A. Rockwell Fisher. The early part of his life was spent in Illinois, Missouri, and Nebraska, where he received his education.

Dr. Fisher attended Doane College at Crete, Nebraska, Kansas City Medical School, Kansas City, Missouri, and was graduated from Northwestern University, Evanston, in 1904. He came to North Dakota to practice following his graduation and was licensed in July 1905.

He did postgraduate work at the Mayo Clinic at Rochester, Minnesota, and studied a year in Europe in 1912. Upon his return, he resumed his practice in Bismarck with the Roan, Fisher and Strauss Clinic, which is now the Missouri Valley Clinic, and of which he was one of the founders in 1909. He withdrew from it in 1918, at which time it became the Roan and Strauss Clinic. He also practiced medicine in Underwood for a few years and was the State Penitentiary physician. He served as head of the Jamestown State Hospital from 1939 until retiring in July 1953.

A veteran of World War I, Dr. Fisher served in the medical detachment of the Army at Camp Dodge, Iowa, and Camp Lewis, Washington. He was a long-time member of the Bismarck Elks Lodge, the Masonic Lodge, and the El Zagal Shrine. He was a long-time member of the North Dakota State Medical Association, was honored as a 50-Year Club member in 1954, and became an honorary member in 1955.

He is survived by his wife, the former Frances Arlene White, whom he married in December, 1914, a son and a daughter.

W. H. WITHERSTINE, M.D.

Dr. William H. Witherstine, 79, prominent Grand Forks physician and surgeon for more than 50 years, died May 11, 1962 at a Rochester, Minnesota, hospital where he had been a patient for the past two weeks.

Dr. Witherstine was born in Dover, Minnesota, on November 7, 1882. He was educated in Rochester, Minnesota grade and high schools, and then attended Chicago University and Rush Medical College in Chicago, receiving his doctor of medicine degree in 1904. He later was made a Fellow of the American College of Surgeons.

He served his internship in the Cook County Hospital in Chicago. He was married June 6, 1906, to Ida Dahlen

at Joliet, Illinois. He came to Grand Forks in July, 1907, and continued the practice of his profession until a few months before his death, although he had curtailed the hours of practice.

During World War I, Dr. Witherstine was a medical officer in 1918 and 1919, located first at Camp Grant Base Hospital, Rockford, Illinois, and later at General Hospital No. 1, New York City.

In Grand Forks, Dr. Witherstine was active in medical societies and in the business, fraternal and social life of the community. He was president of the Grand Forks District Medical Society in 1934 and 1954. In 1954 he was made a member of the 50-Year Club, and an honorary member in 1957.

He was disaster chairman of the American Red Cross chapter in Grand Forks for 25 years, active in the Masons, Scottish Rite, the Shrine (Kem Temple) and Jesters (Court 51). He had been a member of the Grand Forks Elks Lodge for 52 years and one of the charter members of the Grand Forks Country Club.

He is survived by his wife, two daughters, and one son.

W. H. LONG, M.D., Chairman

Committee on Legislation

A number of meetings were held throughout the year. They were held in Bismarck on January 21, January 28, and February 11. Another was held February 17-19 in Chicago in connection with an American Medical Association legislative and political action meeting. Dr. Phil Dahl and Lyle Limond, executive secretary, attended a meeting of the political endeavors group of the North Central area of states June 4 sponsored by the AMA.

At the June 4 meeting Mr. C. Joseph Stetler, director of the legal and social economic division of the AMA, reported that of 10,000 bills introduced in congress, more than 450 pertained to the medical profession. Dr. Dahl reported that major discussion centered about the King-Anderson bill.

Detailed information on the bill is available from Mr. Limond.

In July Dr. Peters and Mr. Limond testified in Washington against the bill. Resolutions against the bill were obtained from the North Dakota Bankers Association, the North Dakota State Pharmaceutical Association, and the North Dakota Jaycees and sent to the House Ways and Means committee.

Drs. P. O. Dahl, Cliff Peters, and O. W. Johnson and Mr. Dan Buchanan and Mr. Limond attended a legislative meeting in Chicago January 27 conducted by the AMA in connection with the King-Anderson bills.

On February 17, 1962, the initial meeting of the committee was held in Fargo relative to AMPAC, a North Dakota organization equivalent, for discussion of the same bills. It was decided that further study would be made of various aspects of the subject. A meeting of the committee was scheduled for March 18 at Jamestown for the purpose of clarifying and bringing to a head the thinking of the various members.

The meeting at Jamestown was comparatively successful, insofar as it was decided to continue with a joint venture possibility of getting members from the North Dakota State Medical Association to become members of the national AMPAC. Likewise, a state organization equivalent in many respects was organized in North Dakota, called COMPACT. The board of directors of the North Dakota COMPACT are: Drs. O. W. Johnson, L. F. Pine, R. W. McLean, B. J. Clayburgh, R. J. Ulmer, P. O. Dahl, H. L. Reichert, J. N. Elsworth, C. M. Lund,

and D. N. Barnard. It was decided that members of the State Medical Association should become acquainted with the purposes of AMPAC and COMPACT and that membership in these 2 organizations be sought. This is being done.

There was discussion of the possibilities of initiating a professional act in the State of North Dakota, whereby permissive legislation would be introduced for the purpose of allowing physicians to incorporate themselves and their partners, thereby improving the possibility of securing fringe and retirement benefits. It was decided, after discussion by doctors and a representative of the legal profession, Mr. William Daner of Bismarck, that a professional corporate act of this nature would be desirable in the state for several reasons. It was indicated that it would be desirable to get other professional groups interested in a practice act of this type to get better support in order to obtain passage at the next legislature.

The chairman recommended that the House of Delegates study this corporate act, and that a recommendation from this body be made to the legislative committee concerning further study and action.

The legislative year is coming up, and from history we know that medical bills have been increasing each and every session. We, as physicians, also have become more politically inclined and are watching legislation that might be either beneficial or detrimental to the medical profession as a whole. It is my impression that there should be closer contact than ever in the coming legislative session between legislators and doctors. We should set up a program, as we have done in the past, whereby a man in each legislative district becomes the key man in that district for purposes of contact with legislators throughout the session. It would be good for medicine to have and show interest in the legislative session by the presence of doctors almost constantly throughout the session, representation to be carried on from all parts of the state through a program set up with our executive secretary and his public relations man.

O. W. JOHNSON, M.D., and
P. O. DAHL, M.D., Co-Chairmen

Committee on Public Relations

The committee is active in attempting to improve the image of organized medicine in its relation to our public. It also is attempting to improve the image of the individual doctor in his relation to other doctors and in his relation to the public.

A résumé of activities to February 1962 and a study by a subcommittee were sent to all doctors in the state February 12, 1962. The résumé follows, signed by Dr. James Mahoney, chairman.

The formation of the new committee on Public Relations was approved in May 1960. The original chairman, Dr. Rodgers, died in September, after hiring George Michaelson to work under our executive secretary, Lyle Limond. In December 1960, a short-range and long-range program was formulated in the committee and first steps were taken to move it into being. Prior to the May meeting of 1961, George Michaelson resigned and we lost several months in selecting our present representative, Daniel Buchanan. At our most recent meeting, December 8, 1961, the committee's feeling was that a report should be submitted to the members of the state association.

We envision a program consisting of two major fields: (1) the improvement of the relationship of medicine as an organized group as well as individuals to society,

and (2) the improvement of the interrelationship among subspecialties in medicine and among medical men themselves. The success of each depends upon the conscious effort of each member of the medical profession.

We are human and have some of the same emotional and personality frailties with which the rest of the human race is plagued. One member of our committee pointed out that if we were capable of fitting the ideal image of the Doctor of Medicine, there would be no need to consider Public Relations. Since this is not possible, we must continue to strive in that direction and improve our image. Dan Buchanan will spend the next six months getting acquainted with as many of you as possible. He will do the same with our legislators, welfare directors, newspaper men, and auxiliary services of medicine. A rapport must be established with the lay people by our official executive representative. Any problems in your various areas will be his problems, and he will be glad to assist you in any manner possible. You are to feel free to write or call our Bismarck office on any of these matters. He will assist in editing or furnishing material for any speeches or, if you have an opportunity to do public speaking and feel you would like a doctor outside your area to assist or talk, notify Mr. Buchanan. If I can be of any assistance, please do not hesitate to drop me a note or call me. The committee also feels that paid advertisements in newspapers will be of value in the future. We believe that the friends of medicine have been neglected and that we should strengthen our bonds with people who have a stake in our successful future as well as those who have a stake in the future of successful free enterprise. This includes dentists, pharmacists, local chambers of commerce, communications systems, and so on. Improvement will take time and result from the example demonstrated to the public.

Our second problem, intraprofessional relationships, is a most sensitive, intangible problem. There will be success if we are able to recognize the basis of our bond in medicine to be our M.D. degree.

In December 1960, the committee selected a subcommittee consisting of Ralph E. Mahowald, M.D., chairman; Robert B. Tudor, M.D.; and Robert E. Hankins, M.D., to study this problem. In May 1961, they reported to the committee, and a copy of this report follows shortly for your consideration. I urge you to ponder this report. The members of this subcommittee or I would be most happy to receive any thoughts on this subject. There are many areas where compromise and consideration are important. I shall quote a few, and I assume you will carry on from there. "Is the general practitioner referring patients to a competent specialty near his home?" "Is the specialty being overzealous in retaining the patient on follow-up care?" "Which specialty field deserves to do a procedure?" "Is there overutilization of consultations involving insurance charges?" "Are the medical directors of insurance companies refusing consultations which would have been utilized had no insurance existed?" "Would one doctor generally feel another incompetent were they 100 miles apart rather than 1 mile apart?" Many items disturb our society, since we are human. A percentage of these problems contaminate our image when viewed by volatile elements outside of medicine. Today's socialistic planners will exploit any dissension, real or imaginary, within medicine. We must strive to be positive, aggressive, and idealistic. We went into medicine to care for the sick and aged, the broken and the dying. May that remain our primary concern in the years ahead.

Following is the report of the subcommittee, of which Dr. Ralph E. Mahowald is chairman:

The task presented to this subcommittee is that of the philosophy of its component members, rather than a dogmatic dissertation of a group. The original premise borders on legislation and documentation of morals, which is a most difficult thing to do without infringement on individual thinking, moral background, and the code of ethics of the individuals to be discussed.

The membership of our profession is made up primarily of individualists in thinking and action capabilities from varied schools. Attempting to make one mold is bordering on the impossible.

Fundamentally, the problem revolves around some of the basic elements of human emotion such as (1) *Jealousy of a professional, social, political, and mental nature*. Egoism is an inherent drive, which no amount of education is capable of directing in an all-conclusive "do-goodism," which will affect our professional relationship with our fellow practitioner. The Golden Rule of doing to others what we would like them to do for or to us is a cliché of long standing and just as truthful today as when first used.

(2) *Economical consideration*. This we all know, in that it is a mandatory part of our life and, to some individuals, the primary measure of success; this can be carried to the extent of gain for the individual, but to the detriment to the profession. This is exemplified by overcharging, overuse of hospitalization, and other insurance factors which are a product of materialism. This point will be a most explosively controversial issue because of the commitment argument of some. We are members of a noble profession, and the care and well-being of the patient should be the primary consideration.

(3) *Lack of Cooperation*. Every member of the profession is faced with the same problem: the practice of medicine. Being individualists, it is unforeseeable that we will all think alike, or arrive at the conclusion by the same route, and it is this gray area that makes us critical of our colleagues. Our loyalty to our chosen life should be adequate to protect each other, but frequently we fail through unfortunate thinking or unexplained remarks—hence lawsuits, dissatisfaction with the profession on the part of the patient, and unwarranted criticism of the profession. We are a group set apart, and should conduct ourselves accordingly for the mutual advantage of the profession, and make it by moral exactitude the noble profession we like to think it is; only the profession can do this.

Possible Solutions: (1) Distinguish between public relations and intraprofessional relations. There is a chasm between these two which prevents consideration of both simultaneously. The first premise must be professional so that a united front will solve the public relations problem. (2) Acceptance on the part of the profession that an intraprofessional problem exists, and these be motivated to its solution. (3) Establishment of basic ethical concepts and their acceptance by the profession. (4) Bring back loyalty to the M.D. degree. Liaison between all specialty groups to keep constant the medical cohesiveness, rather than being split up among the various specialty groups, and allowing that minority to be the driving force. Loyalties must be defined, and brought out in the open and clarified. (5) Guest lecture activity in the local societies by speakers well-grounded in the desired solution; start thinking along these mentioned lines.

Frequently apathy and lack of thinking through of the problem are the greatest stumbling blocks.

No one likes to be preached to, but if a train of thought can be sparked and then encouraged by continued repetition, a great deal could be accomplished.

How many members of the medical profession have attempted to think this problem through? How many conscientiously have thought through a plan of solution? An interesting question.

Following is a resumption of Dr. Mahoney's report:

In August 1961 I attended an excellent program dealing mainly with public relations by the A.M.A. in Chicago. Two basic speeches on public relations from this conference have been distributed at district meetings throughout the state by Lyle Limond and Dan Buchanan. Doctors at the district level are entering into public speaking actively. I know of many instances where they have participated or have been the principal speakers on a variety of subjects. Some of these have been medical and many have been in unrelated fields. It is very important that people consider us active units in our communities as well as in our offices. Some districts are beginning ambitious programs with our friends in the communications field. The First District, as an example of this program, has allocated several hundred dollars and organized a committee to tell medicine's story through local communications, which may include newspapers, radio, and television. This type of programming will have a beneficial effect on smaller districts in the state, since their communications also cover many of our areas.

Dan Buchanan has been actively engaged only six months at the time this report is written. I believe he is an excellent asset to free medicine. I believe his potential will be great if the physicians of North Dakota will utilize his talents. His activities are known to me and will be filed in his report.

I have recommendations which have not been discussed with my committee, but which might be considered by the House of Delegates:

(1) The chairman of the Public Relations Committee should be located in a large center, preferably Bismarck. This will facilitate better communications and coordination with and between the multiple committees of the state society. This will facilitate better communications with and between the executive offices of the State Medical Association.

(2) The committee should be composed of a member from each of our major active committees and any members of our society our president wishes to appoint.

(3) Continue developing active district public relations committees.

These recommendations are made that the Public Relations Committee will have representation on other committees by a professional man as well as our executive directors. This would be of assistance to our committee in having a more complete grasp of the changing public picture. We also should be able to assist other committees in their presentation of their stories to the public. It is sometimes not as important what the story is as how it is presented. This plan might develop a more unified structure.

In closing, I might add it has been my pleasure to serve in this capacity as chairman, and I hope in the coming year we will develop more friends of organized medicine. As they support us, we must support them.

J. H. MAHONEY, M.D., Chairman

Committee on Official Publication

Following the annual meeting, a Committee on Official

Publication was appointed by Dr. Boerth, president, for purposes of evaluating the present official publication for the association and to evaluate other publications which had expressed an interest in becoming the official publication for our society.

In the latter part of May, a letter was received by the chairman from Mr. T. Jerome Enright, managing editor of *Minnesota Medicine*, with respect to plans to expand this journal into a regional medical journal, and with a suggestion that the chairman of this committee contact Dr. C. I. Oppegaard, president of the Minnesota State Medical Association, to determine if the plans of *Minnesota Medicine* met the approval of that association, since it is at present the official organ of this association. A subsequent letter received from Dr. Oppegaard indicated that the council of the association had authorized the board of editors of *Minnesota Medicine* to explore the possibility of making this journal a regional publication and that it had suggested that contacts be made with neighboring states through appropriate committees to pursue that possibility.

In August 1961 a second letter was received from Mr. Enright in which he requested a meeting with our committee and the publication committee of *Minnesota Medicine*. This meeting was held September 23, 1961, in Bismarck. It was attended by Drs. Charles B. Porter, Joseph W. Cleary, and Lee A. Christoferson, representing the Committee on Official Publication for the North Dakota State Medical Association; by Drs. Carl Rice, Stuart W. Arhelger, and David D. Norman, and Mr. Enright, representing *Minnesota Medicine*; and by Mr. John C. Foster, executive secretary of the South Dakota State Medical Association.

The prospectus for this regional medical journal was reviewed by the group representing *Minnesota Medicine*. They were interested primarily to know whether the North Dakota association would be interested in entering into unilateral agreement with *Minnesota Medicine* to make it the official publication of the association prior to the time medical societies of Wisconsin, Iowa, South Dakota, and Nebraska were contacted, since the board of *Minnesota Medicine* contemplated that the regional journal would serve this group of states.

Mr. Foster reported that the South Dakota association was pleased with its present arrangement of publishing its own journal, and doubted that the association would consider abandoning it to enter into an agreement with *Minnesota Medicine*. He reiterated an offer that had been made previously to the North Dakota State Medical Association to join with South Dakota, utilizing the journal as the official organ for the medical societies of both states.

The members of the committee tendered their appreciation to the board of *Minnesota Medicine* for coming to discuss this matter, but unanimously agreed that the North Dakota association would not be interested in entering a unilateral agreement for a regional journal unless an expression of interest had been shown by Wisconsin, Iowa, South Dakota, and Nebraska.

No further correspondence has been received from *Minnesota Medicine* concerning this matter.

The offer tendered by Mr. Foster was acknowledged, and he was advised that it would be brought to the attention of the House of Delegates at the Annual Meeting in June 1962. However, on August 28, 1961, a telephone call was received from Dr. J. A. Myers, chairman of the board of editors of the *JOURNAL-LANCET*, concerning a special issue they wished to publish as a commemorative issue for Dr. Leonard Larson's presidency of the

American Medical Association. Dr. Myers apologized for the fact that *JOURNAL-LANCET* had not stated on its cover that it was the official organ for the North Dakota association and that this identification would be given in future issues.

A subsequent letter from Dr. Myers reiterated the plans for the issue commemorating Dr. Larson and outlined details. This matter was brought before the Committee on Official Publication at its meeting on September 23, 1961, and it was agreed to approve such an issue and to lend whatever support was necessary to assist in its composition. Dean Harwood was appointed by Dr. Boerth to assemble manuscripts for this special issue, which also is to be a North Dakota issue.

A letter from Dr. Myers on March 5, 1962, re-emphasized the desire of the *JOURNAL-LANCET* to receive papers for publication from the physicians of North Dakota and the papers of the speakers invited by the North Dakota State Medical Association to speak at our annual meeting. Action was taken to provide Dr. Myers with a list of the names and addresses of the speakers by our Program Committee so that they could be contacted in advance with regard to the use of their papers for publication in the *JOURNAL-LANCET*.

LEE A. CHRISTOFERSON, M.D., Chairman

Committee on Public Health

The society is happy to have a physician as State Health Officer. He is a man of wide experience in public health, and he should advance public health in the state, together with a cordial relationship with the medical profession.

The concern of the committee has been chiefly the secondary rheumatic fever prophylaxis program.

Two meetings were attended by the chairman—in Bismarck and Dickinson. Both were concerned mainly with the relationship of the pharmacist to the program. It was emphasized that the yellow copy of the registration must be sent to the pharmacist in order that the drugs may be replaced. The physicians must obtain their benzathene, penicillin injection through the pharmacist. It also was pointed out that the penicillin tablets (250,000 units) were a desirable form of prophylaxis.

The chairman, together with Dr. Zimmerman of the Heart Disease Control Program, and Dr. O. V. Lindelow, representing the North Dakota Heart Association, gave a roundtable discussion of the program at the mid-winter institute of the State Pharmaceutical Society at Dickinson in January 1962. I believe this helped to clear up some of the problems of this program.

Recently we polled the members of the Public Health Committee as to the advisability of cooperating in the Cornell University study of fatal accidents in the rural areas of the state. It was decided to cooperate.

Wisconsin passed a law October 7, 1961, requiring two safety belts in the front seat of all cars sold in that state beginning with the 1962 models. It requires that the belts be of a type approved by the Motor Vehicle Department and installed in a manner it approves. The department is following specifications of the Society of Automotive Engineers. Our society might submit such a law to the next legislature.

A 1961 report from the State Health Department on Venereal Disease shows a continuing high incidence of gonorrhea between the ages of 16 and 30.

P. L. OWENS, M.D., Chairman

SYPHILIS CASES BY STAGE AND AGE, 1961

Age	Primary and Secondary	Early Latent	Late Latent	Late Tertiary	Neuro-syphilis	Cardio-vascular	Congenital	Not Given
Total	6	1	19	5	1	2	1	1
Under 1	-	-	-	-	-	-	-	-
1 - 14	-	-	-	-	-	-	-	-
15 - 24	4	-	-	-	-	-	-	-
25 - 44	2	1	6	1	-	-	1	-
45 - 64	-	-	8	2	1	-	-	1
65 and Over	-	-	5	2	-	2	-	-
Unknown	-	-	-	-	-	-	-	-

1961 SYPHILIS CASES BY AGE, STAGE, RACE AND SEX

Age	Primary Secondary	Early Latent	Late Latent	Late Tertiary	Neuro-syphilis	Cardio-vascular	Congenital	Not Given	White	Indian	Other	Male	Female
19	2	-	-	-	-	-	-	-	1	1	-	1	1
22	1	-	-	-	-	-	-	-	-	1	-	1	-
23	1	-	-	-	-	-	-	-	-	1	-	1	-
26	-	-	1	-	-	-	-	-	1	-	-	-	1
27	-	1	-	-	-	-	-	-	-	-	1	1	-
28	1	-	-	-	-	-	-	-	1	-	-	1	-
29	-	-	-	-	-	-	1	-	-	1	-	-	1
30	1	-	1	-	-	-	-	-	2	-	-	2	-
31	-	-	1	-	-	-	-	-	-	1	-	-	1
32	-	-	1	-	-	-	-	-	1	-	-	1	-
35	-	-	1	-	-	-	-	-	1	-	-	1	-
37	-	-	-	1	-	-	-	-	1	-	-	1	-
43	-	-	1	-	-	-	-	-	-	1	-	-	1
45	-	-	-	-	1	-	-	-	1	-	-	-	1
48	-	-	1	-	-	-	-	1	2	-	-	1	1
50	-	-	1	-	-	-	-	-	1	-	-	-	1
54	-	-	1	-	-	-	-	-	1	-	-	1	-
56	-	-	1	-	-	-	-	-	-	1	-	-	1
58	-	-	1	-	-	-	-	-	1	-	-	-	1
59	-	-	-	1	-	-	-	-	1	-	-	-	1
60	-	-	3	-	-	-	-	-	2	1	-	1	2
61	-	-	-	1	-	-	-	-	1	-	-	1	-
65	-	-	1	1	-	-	-	-	2	-	-	1	1
66	-	-	1	-	-	-	-	-	1	-	-	1	-
70	-	-	-	-	-	2	-	-	1	-	1	1	1
78	-	-	1	-	-	-	-	-	1	-	-	1	-
82	-	-	1	-	-	-	-	-	-	-	1	1	-
84	-	-	1	-	-	-	-	-	1	-	-	-	1
88	-	-	-	1	-	-	-	-	1	-	-	1	-
Total	6	1	19	5	1	2	1	1	25	8	3	20	16

Committee on Medical Economics

A few members of the committee met June 20 with the commissioners of the Workmen's Compensation Bureau for discussion of a relative value fee schedule. They were Drs. E. H. Boerth, E. J. Larson, C. H. Peters, and V. G. Borland. While the commissioners were not in favor of adopting the schedule at this time, they were receptive to a change in their fee schedule. We were able to work out an agreeable schedule which was put into effect on October 1, 1961. At the present time, therefore, the doctors in North Dakota are receiving their usual and customary fees for care of workmen under the Workmen's Compensation Act.

The full committee met on December 9 in the Gardner Hotel in Fargo. Mr. Donald Eagles, executive vice-president of Blue Shield, gave a report on Blue Shield's experience with the North Dakota relative value schedule for the past fifteen months. He felt that the two large areas where adjustments should be made were in

the field of in-hospital medical payments and payments for obstetrics.

Figures were presented comparing various items of several relative value plans. The figures in our present schedule were compared with the 1960 California schedule and the professional services index of Blue Shield. Considerable discussion ensued. The matter was tabled temporarily and referred to a subcommittee to be appointed to consider detailed aspects of the various schedules.

Mr. Eagles discussed the possibility of Blue Shield's offering a full service contract to be called Blue Shield plan D, which would be offered to people having more than an annual income of \$7,500. It has been estimated that there are perhaps 10,000 in the state in this category. This item was discussed and tabled pending more detailed requests from the Blue Shield board of directors.

Possible development of legislation permitting physicians to incorporate was discussed. It was suggested that this matter be studied carefully by our legal counsel,

VENEREAL DISEASE CASES REPORTED BY COUNTY, 1961

County	Syphilis	Gonorrhea
Adams	—	1
Barnes	—	2
Valley City	—	2
Benson	1	59
Billings	—	—
Bottineau	—	3
Bowman	—	—
Burke	1	—
Burleigh	1	4
Bismarck	—	22
Cass	—	10
Fargo	5	52
Cavalier	—	1
Dickey	1	13
Divide	—	1
Dunn	—	1
Eddy	—	6
Emmons	—	1
Foster	—	1
Golden Valley	—	—
Grand Forks	2	42
Grand Forks	1	42
Grant	—	8
Griggs	—	—
Hettinger	—	—
Kidder	—	2
LaMoure	—	3
Logan	—	3
McHenry	1	—
McIntosh	—	—
McKenzie	—	—
McLean	3	13
Mercer	—	4
Morton	—	14
Mandan	—	8
Mountrail	1	24
Nelson	—	5
Oliver	1	—
Pembina	2	8
Pierce	—	1
Ramsey	—	7
Devils Lake	—	9
Ransom	—	1
Renville	—	—
Richland	—	6
Rolette	1	49
Sargent	—	3
Sheridan	—	—
Sioux	2	177
Slope	—	—
Stark	—	4
Dickinson	—	4
Steele	—	1
Stutsman	1	9
Jamestown	2	6
Towner	—	—
Traill	—	4
Walsh	—	8
Ward	2	35
Minot	8	27
Wells	—	—
Williams	—	4
Williston	—	7
Total	36	715

VENEREAL DISEASE CASES REPORTED BY MONTH, 1961

	Syphilis	Gonorrhea
January	3	55
February	9	61
March	4	77
April	1	63
May	5	87
June	3	48
July	2	57
August	2	34
September	2	91
October	1	40
November	1	54
December	3	48
Total	36	715

North Dakota gonorrhea rate in 1961 is 113.0 per 100,000 population.

North Dakota syphilis rate in 1961 is 5.6 per 100,000 population.

Gonorrhea increased 18 per cent in 1961 over 1960.

Syphilis decreased 36 per cent in 1961 over 1960.

1961 GONORRHEA CASES BY AGE, RACE, AND SEX

Age	Total	White		Indian		Other	
		Male	Female	Male	Female	Male	Female
Under 10	8	—	2	—	6	—	—
10	—	—	—	—	—	—	—
11	1	—	—	1	—	—	—
12	—	—	—	—	—	—	—
13	—	—	—	—	—	—	—
14	3	—	—	—	3	—	—
15	6	—	1	—	5	—	—
16	18	3	8	—	7	—	—
17	22	4	11	—	7	—	—
18	45	11	10	8	13	1	1
19	42	13	10	4	13	2	—
20	34	12	3	9	5	5	—
21	48	20	7	4	8	9	—
22	35	14	4	7	8	2	—
23	35	11	5	6	10	3	—
24	33	13	3	9	6	1	1
25	39	14	2	10	12	1	—
26	29	10	6	3	10	—	—
27	31	13	3	8	7	—	—
28	26	12	5	6	3	—	—
29	22	6	3	4	7	2	—
30	34	9	2	6	15	1	1
31	14	4	—	5	5	—	—
32	12	4	—	5	3	—	—
33	12	4	—	2	6	—	—
34	15	2	1	4	8	—	—
35	14	4	2	—	8	—	—
36	10	2	1	1	6	—	—
37	18	2	1	7	7	1	—
38	10	3	2	1	4	—	—
39	4	1	1	—	2	—	—
40	7	1	—	2	4	—	—
41	7	2	—	2	3	—	—
42	6	2	1	1	2	—	—
43	6	3	3	—	—	—	—
44	1	—	—	—	1	—	—
45	7	1	2	—	4	—	—
46	4	1	—	2	1	—	—
47	3	—	—	—	2	1	—
48	—	—	—	—	—	—	—
49	4	1	2	—	1	—	—
50 & Over	17	8	3	4	2	—	—
Not Given	33	20	6	4	3	—	—
Total	715	230	110	126	217	29	3

VENEREAL DISEASE CASES BY MARITAL STATUS AND SEX

Group	1961									
	<i>Syphilis</i>									
	Single		Married		Widowed		Divorced		Unknown	
	M	F	M	F	M	F	M	F	M	F
All Ages	5	1	9	11	2	2	2	1	2	1
Under 1	—	—	—	—	—	—	—	—	—	—
1 - 14	—	—	—	—	—	—	—	—	—	—
15 - 24	2	—	1	1	—	—	—	—	—	—
25 - 44	3	1	2	3	—	—	1	—	1	—
45 - 64	—	—	2	1	2	2	1	—	1	—
65 & Over	—	—	2	1	2	2	1	—	1	—
Unknown	—	—	—	—	—	—	—	—	—	—

Group	<i>Gonorrhea</i>											
	Single		Married		Widowed		Divorced		Separated		Unknown	
	M	F	M	F	M	F	M	F	M	F	M	F
All Ages	232	146	92	132	9	15	3	8	6	6	43	23
1 - 14	1	11	—	—	—	—	—	—	—	—	—	—
15 - 24	137	107	17	31	—	—	1	2	3	16	4	—
25 - 44	83	24	59	87	6	12	3	7	4	3	15	14
45 - 64	3	1	9	11	1	3	—	—	—	—	2	2
65 & Over	—	—	1	—	2	—	—	—	—	—	—	—
Unknown	8	3	6	3	—	—	—	—	—	—	10	3

Mr. William Damer, and that the matter be referred to the North Dakota State Medical Association's legislative committee for study and possible action.

Much discussion developed regarding the M.A.A. program in the Welfare Department and its refusal to discuss the development of a separate fee schedule for this group of people. A motion was made and carried that the Medical Economics Committee of the North Dakota State Medical Association suggest to the council of the association that the Welfare Department be notified that after April 1, 1962, no fee schedules will be in existence for any of the several welfare programs in the state, and that the Welfare Board be notified that individual arrangements will have to be made by county welfare boards for payment of physicians' fees. Negotiations with individual physicians on the local and county level for the needs and the requirements of welfare recipients may be preferable to a central bureau which is remote from those receiving the needed care, and also remote from the physicians rendering the needed services.

It was recommended that Mr. Lyle Limond, executive secretary of the association, develop a memorandum of the history of the negotiations the association has had with the Welfare Board during the past years, for distribution to all physicians in the state as well as to various legislators.

The subcommittee, consisting of Drs. V. G. Borland, C. H. Peters, J. F. Houghton, O. V. Lindelow, and M. A. K. Lommen, met in Bismarck on February 2 and 3. Also present were Dr. E. H. Boerth, Mr. Lyle Limond, Dr. A. C. Burt, and Dr. O. A. Sedlak.

The board of directors of North Dakota Blue Shield, meeting on January 20, 1962, had suggested that our committee set fees and take action on two items: the possible development of a service contract for persons with incomes above \$7,500, to be called Blue Shield Plan D, and development of the National Blue Shield Program for the Aged. After considerable discussion, it was decided that the conversion factor of \$5.50 be recommended to the full committee for later action on the proposed Plan D.

Blue Shield Program for the Aged, which has been vigorously endorsed by the American Medical Association, would provide service benefits for single persons whose annual income is \$2,500 or less, and for husband and wife with a combined income under \$4,000. They would be in effect only for persons over the age of 65. The premiums suggested on a national level were set at \$3.20 a month for a single person, and \$6.10 a month for husband and wife. Blue Shield board of directors, at its meeting on January 19, had endorsed this plan with the recommendation that the professional services index be used as a fee schedule, and the conversion factors be adopted which would be comparable to our present Blue Shield Plan A. The subcommittee endorsed the general idea of a national program for the aged but there was considerable disagreement as to the advisability of adapting the P.S.I. schedule to this program. It was recommended that the subcommittee refer this matter to the full committee at a future meeting.

In a discussion of over-all changes in the relative value schedule or adoption of a new one, it was felt that first consideration should be given to payments under in-hospital medical services and payments for obstetrics, since these 2 groups had received a considerable reduction in their fees at the adoption of the schedule some two years ago. Information from the Blue Shield office, after consultation with its actuary, suggested that there might be a possible 5 per cent over-all increase in fees. This was discussed at the subcommittee meeting and comparisons were made between the 3 relative value schedules. It was finally agreed that this increase would not allow enough increase in medical payments or obstetric fees, so it was decided that new comparisons should be developed for general discussion in a full meeting of the committee later.

The full committee met on March 3, 1962, at the Gardner Hotel in Fargo. Several visitors were present, representing various specialty groups in the state. All seemed in opposition to the adoption of the Professional Services Index. The recommendations of the subcommittee meeting were reviewed. Consideration was given first to obstetrical payments. The motion was made and carried that the present relative value schedule be changed to produce a fee of \$70 for Plan A, \$90 for Plan B, and \$110 for Plan C. This allowance may be accepted as indemnity toward total billing for obstetrical services. This represents an indemnity type plan for all obstetrical fees. Much support for this type of plan had been found in a survey of obstetricians, which had been suggested by the Blue Shield board of directors.

There was discussion of payments for in-hospital medical services. A motion was made and carried that under Plan A the unit values would be altered so as to produce a fee of \$9.60 for the first day, \$6.40 for the second day, and \$3.20 thereafter per day. Plan B was altered so as to produce \$12 the first day, \$8 the second, and \$4 per day thereafter. Plan C was altered so as to produce \$13.50 for the first day, \$9 the second day, and \$4.50 per day thereafter.

Since this action in increasing payments for medical services and obstetrical services would now absorb all possible increases permitted at this time, the committee agreed to recommend that surgical fees remain the same, and that we continue to use our present relative value schedule for these fees. A number of items not now present in our relative value scale were to be added. The unit values assigned to these new items were essentially those found in the California 1960 relative value schedule.

The committee refused to set conversion factors for the new proposed Plan D contract. It was moved and carried, however, that if the Blue Shield board of directors proposed to offer a Plan D contract, that no fee schedule be in existence for this contract, and that doctors of medicine would charge their usual and customary fees for services rendered to this particular economic group.

The Blue Shield Program for the Aged was recommended as acceptable if the use of our present Plan A schedule be adopted. The professional Services Index was to be discarded completely under this proposal.

These suggestions were to be forwarded to the Blue Shield board of directors for discussion and approval.

V. G. BORLAND, M.D., Chairman

Committee on Rural Health

The committee held no meetings this past year.

An "Individual Immunization Survey" questionnaire was formulated through the cooperation of Dr. R. E. Hankins of Mott and Dr. Alice Peterson of Bismarck. This survey should be carried out on a countywide basis to determine the number of persons who have been vaccinated. With the cooperation of county homemaker clubs, we hope to complete it. If this program is successful countywide, it should be carried out statewide.

A copy of the individual survey is shown below.

M. S. JACOBSON, M.D., Chairman

(The transactions will be continued in the December issue)

INDIVIDUAL IMMUNIZATION SURVEY (Please complete and return)

Name	Age	Sex
Address	Occupation	
If student, name of school		
Poliomyelitis immunizations?	Yes	No
Date		, if yes, complete: Date
1st shot		3rd shot
2nd shot		Last booster
Smallpox vaccination with a "take" (scar) evident? Yes No		
If yes, date		
Revaccination?	Yes	No
Diphtheria, Whooping Cough, Tetanus completed series?		If yes, date
Yes	No	If Yes, date
Booster?	Yes	No
		If Yes, date
Tetanus series?	Yes	No
		If Yes, date
Booster?	Yes	No
		If Yes, date
Mantoux test?	Yes	No
		If Yes, date
If Yes, results of test		
Date of last chest X-ray		

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1. Kolodny, A.L.: *Dis. Nerv. System* 22:151 (Mar.) 1961.

For prescribing information, please see *PDR* or available literature.

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Book Reviews . . .

The Skin: A Handbook

RICHARD L. SUTTON, M.D., 1962. *Garden City, New York: Doubleday & Co.* 350 pages. \$4.95.

This book is, as the title states, a handbook. It was apparently designed to provide general information regarding the skin in health and disease. It also provides, in survey manner, clear and concise coverage of more common skin diseases, as well as many rare dermatoses.

The author's avowed purpose is to provide a book for any person concerned with a skin problem. It would not ordinarily be considered sufficient source material for medical students or physicians; it is intended for the interested lay public and patients, as well as for nurses and public health and paramedical personnel.

Considerable general information about physiology and structure of the skin is supplied in the forepart of the book. Dr. Sutton has segmented his coverage of the dermatoses on a causative basis—namely, chemical, viral, bacterial, animal, physiologic and psychic combined, and unknown causes. His literary style is effortless and colorful.

In considering the usefulness of this book for the physician, a number of deficiencies are evident, such as the absence of specific detail and description, lack of discussion of abnormal variants of many of the dermatoses, and the absence of references for further study. Also, there are no illustrations.

In summary, the book is an inexpensive, readable, and concise source of information which appears to be designed primarily for the lay public and is of less specific value for the physician.

RALPH REEDS, M.D., and MILTON ORKIN, M.D.
Minneapolis

Early Detection and Diagnosis of Cancer

WALTER E. O'DONNELL, M.D., EMERSON DAY, M.D., F.A.C.P., and LOUIS VENET, M.S., F.A.C.S., 1962. *St. Louis: C. V. Mosby.* 286 pages. Illustrated. \$12.00.

This book represents a new and refreshing approach to a discussion of cancer detection methods. The text is based on experience at the Strang Cancer Prevention Clinic of Memorial Hospital, New York City, with approximately 360,000 cancer detection examinations in over 100,000 patients seen in this clinic since its founding. The format of the book is excellent and the organization of material is logical and in a correlated sequence.

The first portion of the book discusses the cancer problem along with the basic requirements of a good cancer detection examination. Line drawings accompany the text illustrating equipment for and steps in the examination, basic requirements of an office laboratory, and the methods of obtaining specimens for the various examinations, such as Papanicolaou smears and tissue biopsies. Methods of performing the necessary laboratory work are also depicted.

The second portion of the book is divided into chapters, each of which discusses cancer as related to a particular system of the body. Included in each discussion are a general description; statistics on the relative frequency of this type of cancer; the incidence in men and women; deaths in men and women and percentage

of the total mortality from cancer; comparison of the rate and ratio; the trend during the past ten years; and finally, the age groups in which most cases occur. Each chapter includes information as to the clinical manifestations of the disease in these various systems, the more specific types of examinations and laboratory procedures to be done in the diagnosis of various lesions, and a brief discussion of pros and cons for each type of therapy.

One of the chief attributes of this book is the elimination of extraneous material and discourse. This makes it an excellent reference work for the examiner's office.

I believe this book would be invaluable to anyone doing cancer examinations, be he specialist or general practitioner.

Since the report is based primarily on the experience in one clinic, the bibliography is short. However, the standard sources of material are listed, and these in turn lead to a more extensive supply of information.

D. E. STEWART, M.D.
Crookston, Minnesota

Practical Electroencephalography for the Anesthesiologist

VERNE L. BRECHNER, M.D., RICHARD D. WALTER, M.D., and JOHN B. DILLON, M.D., 1962. *Springfield, Ill.: Charles C Thomas.* 107 pages. \$6.50.

In these times of increasing dependence upon automation and the resultant deterioration of regard for the acumen which can be acquired only by practical experience, it is heartening to see that the authors of this useful volume point out that the electroencephalograph cannot do the job in anesthesia by itself but that the aid of a person is required. They also observe that the reliability of the electroencephalograph is not absolute and, in fact, is not so impressive as some have thought in the matter of providing exact information. They mention the factors which can cause variations from the normal when the causes of variations are invisible. They refer frequently to the work of Faulconer, Bickford, Courtin,^{*} and Kiersey, who had more confidence in the uses of electroencephalography in anesthesiology than is entertained by the authors of this book. One of the best illustrations in the book is figure 7 of chapter 4, which is an outline of cerebral circulation.

This book is printed on good paper, is well indexed, and has innumerable reproductions of electroencephalographic tracings, many of which can be seen better with a reading glass than in the size in which they appear in the book. The text is easily read. The book should be of interest to those who wish to learn more about the use of the electroencephalograph during anesthesia than is to be found in papers and other such sources.

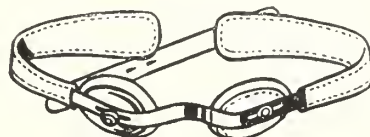
JOHN S. LUNDY, M.D.
Chicago

^{*}I remember well when some of the first electroencephalographic tracings were made by Courtin at the Mayo Clinic as a result of Bickford's work on animals. Courtin asked me to look at a tracing that had been made during anesthesia, pointing out the several depths of anesthesia, and said, "What shall we call them?" I suggested that such depths of anesthesia be called "levels," and I added that they represented new parameters in anesthesiology and should not be confused with Guedel's "stages" and "planes" of anesthesia.

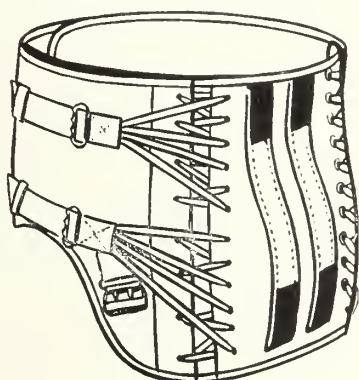
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Whether you prescribe

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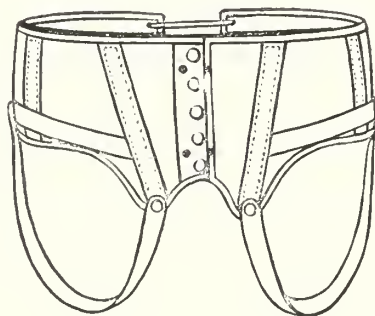


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BOOK REVIEWS

(Continued from page 16A)

Shock: Pathogenesis and Therapy

K. D. BOCK, editor, 1962. Berlin: Springer-Verlag. 387 pages. Illustrated. 37.50 DM (approximately \$5.50). An international symposium, Stockholm, June 27-30, 1961, sponsored by CIBA. New York: Academic Press, Inc.

An excellent and detailed review of shock, its pathogenesis and therapy, is presented. In this international symposium, a special effort is made to integrate the basic and clinical sciences. This gives the reader the rare opportunity of following the development of theories about various aspects of shock from the bedside to the animal laboratory and back to the bedside—all within 1 volume.

Each of the 31 individual papers collected from the symposium is clearly written, adequately illustrated, and followed by a complete bibliography and critical discussion section. The symposium itself has been exhaustively referenced into a subject index, which increases the usefulness of the volume to those interested only in isolated areas of the shock problem.

The subjects covered by the symposium include: a definition of shock; the hemodynamic, endocrine, renal and metabolic changes during shock; myocardial shock; allergic and radiation shock; and, finally, the therapy of shock.

As an aid to the reader, the chairman, U. S. von Euler, has integrated (in his closing remarks) the material covered by the symposium. This reviewer would recommend reading the closing remarks before reading the book itself. In addition, the papers presented by Drs. Rushmer, Fine, Greeg, Lillehei, Gelin, Nickerson, and Ström serve as such a good general review that the reader may wish to read these before turning to the other excellent papers which cover various aspects of shock in greater detail.

This book is recommended for practicing physicians. Many of them will want to own this book because of the detailed information given in the section on therapy. All measures and drugs currently used in shock therapy are reviewed; the indications and contraindications are given, as well as dosages and other specific information. The usefulness of this section on therapy alone will justify the purchase of this book.

ARTHUR F. BICKFORD, M.D.
San Francisco

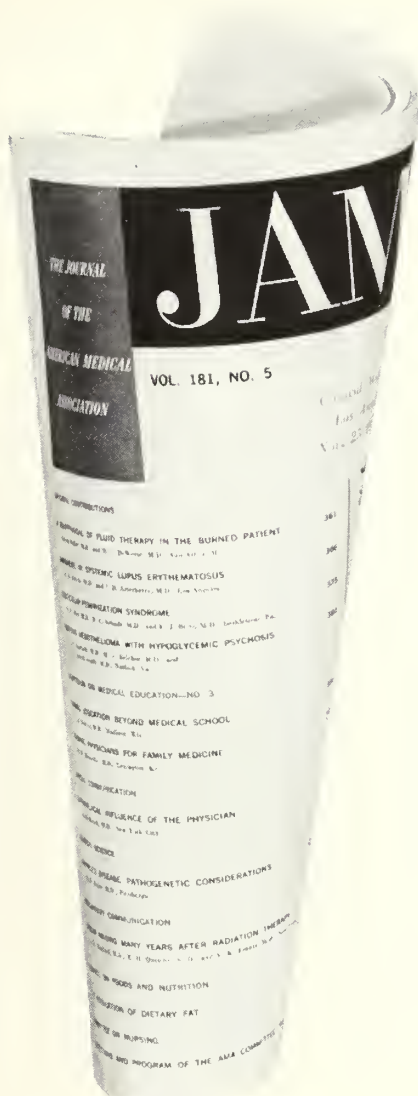
Martini's Principles and Practice of Physical Diagnosis

Revised by YALE KNEELAND, JR., M.D., and ROBERT F. LOEB, M.D., third edition, 1962. Philadelphia: J. B. Lippincott Co. 275 pages. Illustrated. \$4.75.

The immediate appeal of this small book—*multum in parvo*—is, for the most part, achieved by its compressed information and its simplicity. For example: Why is it hard to percuss the heart borders in the chest? Is there a specific way to do so? What are the pitfalls? The answers lie in a simple series of maxims, acoustic principles, which are laid out in an early chapter.

The recognition of subsurface masses depends on our appreciation of pitch, intensity, and duration of reflected sounds. The pitch will depend on the base diameter of the zone of vibration. But since heart, bone, and wide flat masses intensify and deepen sound, rib percussion would be deceptive and uninformative. With intercostal percussion, shallow lung, less than 4 cm. deep, gives use-

(Continued on page 20A)



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From the Aug. 4, 1962 issue of The Journal of the American Medical Association.

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BOOK REVIEWS

(Continued from page 18A)

ful information in pitch variance. However, deeper covering of lung allows no variance in pitch and hence information.

Too complicated so far?—then consider this. Irregular contours of the chest, such as the breasts, throw off all observations. And an emphysematous chest deepens lung tissue and hence its tones. These potential errors must be considered in the final evaluation. Yet, careful observation and quiet intercostal percussion give meaningful information.

Percussion can be a test of experience as well as of character: "Nothing betrays the beginner more completely than an inelegant technique of percussion." "Rigid intellectual honesty is essential lest the examiner (by varying his technique) produce the expected or feared result of percussion."

Many of us have learned physical diagnosis by the preceptorial patterns of demonstration and identification; we are shown a physical sign and it is explained clinically and physiologically. Physical diagnosis has been an art, using the senses—seeing, hearing, and feeling. In this book some basic science is injected and where simple physical laws are used to explain phenomenon, it is quite superior. Where it flounders into words and allusive terms, it is just another catechism.

There are minor flaws which do not detract from the book. The paucity of illustrations, for reasons of economy and brevity, can be understood, but why write one and a half pages of description of topographic points and lines, when a half-page line drawing would do it better? Again, some descriptive terms for pulmonary signs have a nagging vagueness. The authors have dismissed some of Skoda's rhetorical terms; they might also relegate to a footnote such terms as "crepitant rales." There are better classifications.

Physical diagnosis is not all of diagnosis, as we learn from Martin's introduction: All medical thought must consider the interweaving of the *physical* and *psychic* processes which form the mosaic of the disease. To achieve his share of understanding of the former, every medical student should master this book, and every physician should read it.

FRANK ANKER, M.D.
Oakland, California

Synopsis of Obstetrics

CHARLES E. MCLENNAN, M.D., *sixth edition, 1962. St. Louis: C. V. Mosby Co. 464 pages. Illustrated. \$6.75.*

The previous editions of this popular textbook have been widely read by medical students and used for review by countless others. The author has brought the sixth edition up to date and, as usual, has done a superb job.

The content is clear and concise. The views expressed by Dr. McLennan are well accepted and follow the present-day teaching of obstetrics. Recent advances such as in cervical incompetence, the treatment of hypofibrinogenemia associated with pregnancy, and others are briefly mentioned. No detailed explanations are made since this volume is primarily written in outline form.

The general appearance of the book and its illustrations are excellent. The chapter headings and divisions are clear and follow a well-devised format.

This book should be widely accepted by medical students and physicians interested in a quick, yet complete and systematic, review of current obstetric practice. To these groups this book is highly recommended.

FRED A. LYON, M.D.
Minneapolis

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SERVING THE MEDICAL PROFESSION OF MINNESOTA,
NORTH DAKOTA, SOUTH DAKOTA, AND MONTANA

Series on PSYCHIATRY for the PRACTITIONER

A State Hospital Program for Alcoholism and Drug Addiction

VERA M. EIDEN, M.D.

St. Paul, Minnesota

WILLMAR STATE HOSPITAL, Willmar, Minnesota, was established in 1907 as a hospital for the treatment of alcoholism and drug addiction. In 1917, a second section was opened for the care of mentally ill patients. Since that time, the hospital has served a dual function, but the 2 programs have developed relatively independently, especially since 1950.

Currently the program for alcoholism and drug addiction is housed in separate buildings and staffed independently, although it is under the same hospital administration and it shares the same ancillary services.

The state of Minnesota is divided into 7 mental health districts, each serviced by a state hospital and one or more mental health clinics. Willmar State Hospital receives men for the treatment of alcoholism or drug addiction from 6 of these mental health districts and women from the entire state. There is a total of over 1,600 men and women entering the hospital each year for treatment in this program.

The general principles employed in the treat-

ment of alcoholism at Willmar were described in a previous article.¹ This paper will discuss the organization of the Willmar program in order to give a picture of what the individual patient experiences while in the hospital.

ADMISSION TO THE HOSPITAL

Over 60 per cent of the men and women entering the alcohol or drug addiction program telephone the hospital to make arrangements for their admission on a voluntary basis. Usually a bed will be available on the day they decide to enter, but occasionally it may be necessary to wait a few days. Patients come to the hospital unaccompanied or are brought by relatives or friends, sometimes members of Alcoholics Anonymous. About 40 per cent come to the hospital accompanied by the sheriff following a commitment by the probate court. Following admission to the hospital, voluntary admissions and those entering on court commitment are treated similarly. Each is expected to remain for the sixty-day program unless severe personality problems or physical impairments indicate need for a longer stay.

On admission, each patient receives a thorough physical examination, including chest roentgenogram, blood Wassermann, hemoglobin determi-

VERA M. EIDEN was formerly medical director of the Willmar State Hospital, Willmar, Minnesota. She is presently director of the Department of Neuropsychiatry, Ancker Hospital, St. Paul, and professor of psychiatry, University of Minnesota.

nation, and urinalysis. This evaluation is carried out in the medical-surgical service to which each patient is admitted.

About half of those entering do not require any special medication for alcohol withdrawal; the others need medication for tremulousness and restlessness. The majority of these receive methaminodiazepoxide (Librium), and an occasional patient, chlorpromazine (Thorazine). Only occasionally does a patient need parenteral fluids or supplementary vitamins. On this regimen, most patients are on house diet within twenty-four hours. Vomiting is a rare occurrence, as is delirium tremens.

Willmar State Hospital, including all receiving units, is 100 per cent open; that is, there are no locked wards. With the above regimen, patients can be handled satisfactorily in the open medical-surgical building which is similar in its organization to any general hospital.

ASSIGNMENT TO THERAPY PROGRAM

Within twenty-four hours of admission, the patient is visited by a counselor on alcoholism. These are men who have been active members of Alcoholics Anonymous for many years who now work in the Willmar program as full-time staff members with civil service status. The counselor reviews with the patient the circumstances leading to his hospitalization, his attitude toward his problem, and the history of his illness, including former hospitalizations and efforts at receiving help. Information is also gathered by the social service department concerning his occupational history, medical history, family history, marital history, educational background, and religious affiliations. On the third morning after admission, this material is reviewed and the patient is interviewed by the staff. Tentative psychiatric and somatic diagnoses are established. It is decided whether he should enter the individual psychiatric treatment unit of the alcohol program or be assigned to psychodrama or to one of the counselor's groups. Occasional cases remain under the care of the medical-surgical service for a longer period before entering the alcohol program proper.

The new patient is also given a work assignment by the patient placement officer. Each patient is expected, during his stay in the hospital, to spend about six hours a day on a work assignment. Because of budget limitations, this contribution of work is essential for the proper running of the hospital. It also brings to light many of the individual's difficulties in working cooperatively with others, in accepting work responsibility, or in authority relationships.

During his stay at the hospital, the patient, if he is a man, lives in a ward set aside for the men from his section of the state. Men from adjacent counties which are in one receiving area live together while in the hospital and are assigned to the same counselor's group. Later they will attend the same or nearby Alcoholics Anonymous groups in the community. This encourages the formation of friendships which will be mutually supportive at the community level and increases the likelihood that A.A. attendance will be continued later. It also gives the counselor a better opportunity to maintain contact with his patients, since he visits the A.A. groups in this particular section of the state.

THE THERAPEUTIC PROGRAM

Each counselor has 3 groups of 10 patients. He meets with them as a group twice a week for a total of 12 to 14 meetings; in addition, he meets with the members of the group individually, as indicated. He serves as a group leader in the discussions of problems of alcoholism, principles of Alcoholics Anonymous, and the difficulties in interpersonal relationships experienced by the alcoholic within and outside the hospital.

Men who are assigned to the individual psychiatric treatment unit of the alcohol and drug addiction program meet with a psychiatrist for regular psychotherapeutic sessions (individual and group) throughout their stay. They also meet twice a week with a counselor for group discussions.

Certain selected patients are assigned to psychodrama. Some of these are also seen in counselors' groups. In these sessions, members of the group, under the guidance of a therapist, take their turns in acting on a stage various problems associated with alcoholism. The other members of the group serve as audience and discuss the situations dramatized and clarified through the action on the stage. Psychiatrists, psychologists, social workers, counselors, and chaplains function as therapists and co-therapists from time to time.

The entire group of patients in the alcohol and drug addiction program, following withdrawal therapy, meets at 8:00 A.M. every morning for an orientation lecture. Thirty-two lectures are given in series on a five day per week basis, then repeated. Thus, while each patient enters this series on the date determined by his admission, each one has an opportunity to attend the entire course of lectures. Each staff member—medical director, psychiatrist, psychologist, social worker, alcohol counselor, or chaplain—discusses whatever topic is most appropriate to his area of

specialization. Basic information is given concerning alcohol, alcoholism, and problems of personality functioning. Occasional appropriate movies are shown.

There is also a scheduled program for evenings. On Monday, the chaplain discusses spiritual problems. On Tuesday, visiting A.A. groups schedule meetings to introduce the patients to principles of Alcoholics Anonymous and give them opportunities to meet members with whom they may have association after leaving the hospital. On Wednesday, a counselor holds a question-and-answer session for free discussion of any problems raised by the group. Thursday night is "Toastmasters' Night," to develop skills in self-expression in public. Each Friday, a counselor discusses 2 of the A.A. steps so that the 12 steps are discussed systematically over a six-week period. Saturday night another A.A. meeting is held under the leadership of visiting A.A. groups.

All members of the staff of the Alcohol Program meet on a weekly basis to share experiences and information in the field of alcoholism and to discuss administrative problems. Also, there is an organized, two-year, in-service training program for alcohol counselors to assist them in methods of handling groups and in dealing with personality problems.

At any one time there are about 210 men in the program and 30 women. For this reason, the women's program is organized somewhat differently than the men's. Alcohol withdrawal for women occurs in their own cottage in which they stay throughout the sixty-day program. One psychiatrist and one counselor are assigned full-time to this cottage. The psychiatrist takes care of alcohol withdrawal, sick call, and any special needs for individual psychotherapy.

RESPONSIBILITY FOR SELF-CARE

The men are housed in units where they are given substantial responsibility for self-care. Patient councils plan much of the ward organization, the assignment of housekeeping tasks, mail distribution, and recreation programs. They take responsibility for their own clothing and personal care. Medical needs are handled through office visits by appointment with a member of the medical staff who is also the physician in charge of withdrawal therapy. Each man takes responsibility for having any prescription for medication filled at the hospital pharmacy; he carries his own week's supply of medication and takes responsibility for taking it as ordered. No tranquilizers, sedatives, or habituating drugs are ordered for men while they are in

the alcohol program. If a need for any such medication arises, a man is transferred to one of the nursing care units of the hospital where such medications are given under nursing supervision.

Every effort is made to encourage each patient to make an appointment with the chaplain so that he can complete the fourth and fifth steps of the Alcoholics Anonymous program while he is still in the hospital. Not all do so, as this is entirely voluntary; however, every encouragement is given to each patient to complete this personal inventory and share this with another person since this is considered one of the crucial parts of the program.

Disciplinary problems that arise are discussed, usually by the patient councils or by the counselor's group. If no solution is found in this way, the matter is brought before a disciplinary board consisting of 3 members chosen from the staff. It is only rarely that such action need be taken as most difficulties that develop in the group living situation are worked out by the men and women themselves.

EVALUATION OF THE PROGRAM

It is difficult to get an accurate evaluation of the effectiveness of the program. This would require careful follow-up studies, locating sizable numbers of patients, preferably at the end of two to five years after return to the community.

Members of the staff who keep in touch with community A.A. groups are frequently heartened by the number of the graduates of the program they find maintaining sobriety and active affiliation with A.A. groups. Others who rarely visit in the community become discouraged by those who have frequent returns to the hospital. In recent years, between 58 and 62 per cent each year are first admissions. Only a conspicuous minority have multiple returns.

Accurate estimates of the effectiveness of the program must await the granting of funds for adequate follow-up studies; however, experience shows that substantial numbers of persons who have been disabled for ten to fifteen years with this chronic illness are started on the road to sobriety during their stay at Willmar. In addition, many of them gain increased awareness of themselves and greater understanding of their personal problems.

A letter is written to the spouse of the alcoholic, inviting him or her to attend a regular meeting held Sunday afternoon to discuss problems of alcohol and alcoholism and the work of Al-Anon, an organization for nonalcoholic spouses of A.A. members. Members of the local

Al-Anon organization cooperate in this program. Names of members of local Al-Anon groups are given and the spouse is urged to make contact with such groups in order to help him handle more adequately the problems arising through his association with an alcoholic.

In the future, it is hoped that there will be community-based counselors on alcoholism in each of the mental health districts of the state so that these can work in cooperation with the hospital-based counselors for better follow-up of

men and women who have returned to the community. It is also hoped that, through various mental health agencies in each of the mental health districts, more professional help will be available for the wives and children of alcoholics, and that progress will be made toward increasing understanding in the community of the problem of alcoholism.

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PREDISPOSITION for a peculiar type of malignant lymphoma seems to accompany the Chédiak-Higashi syndrome in children. Whether lymphoma inevitably develops from the syndrome is still to be determined. Studies were made of two siblings with the syndrome. One has since died of malignant lymphoma, the other is still alive without lymphoma. A review of the literature disclosed that among the 16 cases reported, several had malignant lymphoma and that after development of hepatosplenomegaly most died before reaching the age of seven years. The Chédiak-Higashi syndrome is an anomaly of leukocyte granulation. Large eosinophilic, peroxidase-positive inclusion bodies appear in the myeloblasts and promyelocytes of the bone marrow. Large granules are found in the more mature cells of the neutrophil, eosinophil, and basophil lines. Many lymphocytes from peripheral blood contain small peroxidase-negative inclusion bodies. Characteristically, patients have partial albinism, photophobia, and shifting nystagmus on exposure to light. Also, they may be highly susceptible to infection. In the two siblings studied, white blood cell function and antibody function were normal. However tryptophan metabolism studies disclosed an unexplained lack of 5-hydroxytryptamine in the peripheral blood, even after 1-tryptophan and 5-hydroxytryptophan loading. A pathologic diagnosis of malignant lymphoma may be made on the basis of destruction of normal lymph node and spleen architecture.

A. R. PAGE, H. BERENDES, J. WARNER, and R. A. GOOD. The Chédiak-Higashi syndrome. *Blood* 20: 330-343, 1962.

CYSTIC HYGROMA, a benign overgrowth of lymphatic vessels, is best treated by complete excision. The tumor appears early in life as a nontender, soft, semi-fluctuant, moveable mass, usually in the neck, but sometimes in the thorax, axilla, groin, or abdomen. Complete surgical removal presents technical difficulties. The cyst must be carefully dissected so that the thin walls will not be torn. Complete removal is almost impossible once the mass has collapsed. Any islands of tissue that are left act as foci for recurrence. If the tumor cannot be completely removed, the cavity is packed with iodoform gauze to sclerose the membrane lining and reduce drainage. Irradiation or radon seed implantation is used for recurrences when radical surgery is not feasible.

M. GALORE, E. S. JUDD, P. E. PEREZ, and E. G. HARRISON, JR. Results of surgical treatment of cystic hygroma. *Surg., Gynec. & Obst.* 115:319-326, 1962.

Aplasia of the Pulmonary Artery

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OUR PURPOSE in presenting these 2 cases of pulmonary artery atresia is to emphasize the necessity of a thorough, integrated study including angiocardiology for congenital heart disease in infancy.¹ The effectiveness of cardiography is especially noted in our experience with cyanotic babies as opposed to the relative difficulty with oximetry and dye dilution curves in infants. Frustration of these catheter attempts often stems from technical problems and hazards in sampling from a small child. Very striking is the rapidity, ease, and success of angiocardiology and especially selective cineangiocardiology for demonstration of these defects with right-to-left shunt. Features of the selective angiocardiology are most helpful in determining prognosis or surgical approach and its urgency.²

CASE REPORTS

Case 1. S.H., a white male child, was born on June 3, 1960. He was mildly cyanotic at birth, but without heart murmur or thrill. These findings were confirmed by one of us at 3 days, at which time the electrocardiogram showed a rate of 184 and right ventricular preponderance. At 6 months of age, the child was still cyanotic. Marked bossing of the parietal bones with bulging of the anterior fontanel and wide cranial sutures were present. Hemoglobin was 16.5 gm. and red blood cell count was 4,900,000.

At 13 months of age, the child was admitted to the Bismarck Hospital because of increasing cyanosis and cough. Clubbing of the fingers and toes was present, along with a very faint cardiac murmur which was difficult to define. Weight was 14 lbs., and hemoglobin was 14.2 gm. Roentgenograms of the chest revealed the lungs to be clear with diminished vasculature. At consultation, differential diagnoses of tetralogy of Fallot, pulmonary atresia, pulmonary arterial fistula, systemic venous drainage into the left atrium, Ebstein's anomaly, and methemoglobin anemia were entertained. Cardiac catheterization with angiocardiology was advised.

Under premedication of 1.3 mg. morphine sulfate and 60 mg. sodium phenobarbital, the child was lightly strapped to a circumcision board and 13 mg. of Vistaril (hydroxyzine pamoate) was administered intramuscularly. The area of the vein was infiltrated with 1 per cent

Novocain (procaine hydrochloride). A brachial vein cut-down was performed and a No. 5 injecting catheter was inserted. This was then passed under image intensifier guidance into the right atrium. Its course appeared to be slightly left of the normal superior vena cava position. The tip of the catheter lodged near the tricuspid valve area at the level of the diaphragm. All attempts to enter an area resembling the right ventricle, either by fluoroscopic appearance or by pressure recording, were futile. The catheter tip was then positioned at the upper edge of the right atrial area, which appeared to be a combined vena cava and coronary sinus position (figure 1), and forward angiocardiology was performed with the patient in the anteroposterior projection. Eleven per cent of Renovist (69 per cent diatrizoate) at 37° C. and 6 kg. per square centimeter pressure were injected in a one-second period, and 13 films programmed at 3 per second were obtained with the rapid cassette changer. At this point, a second attempt to pass the catheter to the right ventricle was unsuccessful; fluoroscopic image and pressure monitoring indicated right atrial level at all times. A lateral angiocardiology study similar to the above was then repeated. The patient tolerated the procedure without apparent increase in cyanosis or other difficulty.

The angiocardiology (figures 2 and 3) revealed absent pulmonary artery (atresia), pulmonary circulation via the bronchial arteries, single large aorta (pseudo-truncus), probable single ventricle or interventricular septal defect, left sided superior vena cava entering the atrium via coronary sinus, and atrophic left atria. One month later thoracotomy was being considered when the baby expired at 14 months of age.

The pathologic report was summarized as follows: Cause of death: congenital heart disease; anatomic diagnoses: congenital absence of pulmonary valve and artery, interventricular septal defect, patent foramen ovale, hypertrophy of ventricular myocardium bilaterally, solitary kidney, atresia of distal segment of left ureter, left hydro-ureter, focal edema, congestion and emphysema of lungs, and passive congestion of spleen. The pathologist's comment was that the absence of the pulmonary valve and pulmonary truncus, in addition to the absence of the ductus arteriosus, resulted in a pulmonary circulation through bronchial arteries and return of aerated blood through the pulmonary veins.

The autopsy confirmed that this patient could not have benefited by surgery.

Case 2. D.H., an 8-week-old female infant, was referred by the family physician because of a heart murmur first noted at the time of the six weeks' checkup. Apart from respiratory infection at 6 weeks of age, the infant had been well. There was no family history of congenital heart disease.

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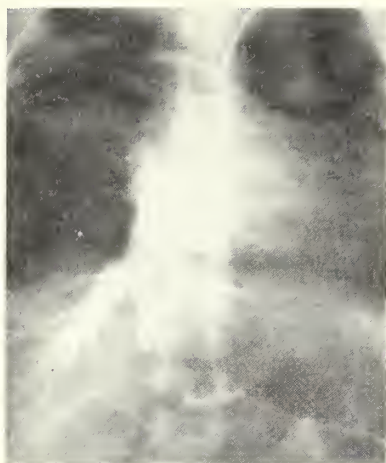


Fig. 1. (*left*) Early angiocardio-graph, anteroposterior (case 1)



Fig. 2. (*right*) Angiocardio-graph, anteroposterior (case 1)

Examination revealed marked grayish cyanosis, a pulse of 150, and grade II systolic ejection-type murmur at the left sternal border in the second and third interspaces. This was also heard faintly over the posterior left chest, although pulmonic second sound was not clearly defined. The lungs were clear and the remainder of the physical examination was normal. The electrocardiogram showed pulmonale-type P waves and right ventricular hypertrophy. On roentgenographic examination, the heart was hoot-shaped with marked concavity of the pulmonary artery segment indicating small to absent pulmonary artery trunk. Diagnoses of tetralogy of Fallot, truncus, and tricuspid atresia were considered.

On August 22, 1961, the day following hospital admission, under preanesthesia consisting of 1 mg. morphine sulfate and 60 mg. sodium phenobarbital, the child was brought to the heart catheterization laboratory. The right inguinal area was infiltrated with 1 per cent Novocain, and an incision was made over the region of the fossa ovalis. The greater saphenous vein was isolated and dissected centrally. The vein was of such small size that a 20-gauge blunt needle was the largest instrument that could be inserted into its lumen and tied in place. Using a pressure syringe, 5 cc. of Renovist at 37° C. was injected at a pressure of 2½ kg. per square centimeter. Thirty films were obtained, programmed at 3 per second, using the rapid cassette changer. After the initial anteroposterior view, a second injection was carried out

to obtain views in the lateral projection. The 20-gauge needle was then removed from the saphenous vein, which was ligated close up to the femoral vein. The infant remained cyanotic throughout the procedure, and there was no change in her general condition.

The forward angiocardio-graph obtained (figures 4 and 5) gave clear definition of the main chambers of the heart. The right ventricle was seen to drain solely to the aorta, with rapid transit of all of the opaque media from the right ventricle to the aorta. No clearly defined pulmonary artery could be identified in either the anteroposterior or lateral views. Apparently the major circulation to the lung arose from bronchial arteries. The possibility was considered, but deemed unlikely, that a very tight pulmonic stenosis could result in such a streaming of flow of the blood, such that there would be no opacification of an atretic pulmonary artery. However, an imperforate pulmonic valve with intact artery was not ruled out. This baby expired at home, one month after the angiocardio-graph. No autopsy was done.

DISCUSSION

The cases cited are in a differential diagnostic group including the following defects: tetralogy of Fallot, pulmonary atresia with pulmonary blood flow via patent ductus, pulmonary atresia with circulation via the bronchial arteries, pul-



Fig. 3. Lateral (case 1)



Fig. 4. Anteroposterior (case 2)



Fig. 5. Lateral (case 2)

monary arteriovenous fistula, systemic veins draining into the left atrium, Ebstein's anomaly of the tricuspid valve, and other rare congenital cardiac defects. The differential feature of tetralogy of Fallot is that there should be a systolic murmur present along the left sternal border representing flow through the infundibular stenosis. Usually pulmonary arteriovenous fistula, if large, will show on the roentgenogram. Systemic veins draining into the left atrium are rare, but they create a similar clinical picture with normal heart size and no murmur. The anomaly of the tricuspid valve, called Ebstein's anomaly, can cause cyanosis in early infancy without striking murmurs. The absence and faintness of murmur appeared to be the only feature indicative of absent pulmonary trunk in case 1. Should the infant reach the age of 2 to 3 years, one would expect the presence of a machinery, to-and-fro, systolic-diastolic murmur resulting from the florid development of bronchial arteries.

In aplasia of the pulmonary artery, sometimes termed "pseudotruncus," the absence of the murmur in early infancy presumably may be accounted for by the fact that the 2 ventricles both eject into the aorta with no flow across the pulmonary valve. When pulmonary blood flow is via bronchial vessels in young infants, such flow is usually silent. Electrocardiographic findings of right ventricular hypertrophy are usual in these cases and, while roentgenographic interpretation in the infant is difficult, the sparsity of pulmonary vasculature should be evident. The most certain aid to definitive diagnosis is selective angiocardiology from the right ventricle, preferably cineangiocardiology.

A truncus arteriosus with reduced pulmonary blood flow shows prompt opacification from the right ventricle. Unless the anomalous vessels of

the collateral circulation are demonstrated, the angiocardiology may fail to differentiate a truncus arteriosus with reduced pulmonary blood flow from a tetralogy of Fallot with aplasia of pulmonary artery. It has been contended that "this is a distinction of little practical importance as it denotes only slight functional, anatomic, and therapeutic difference and is of no clinical importance."² The pulmonary arterial tree in pulmonic trunk atresia has been recently described,³⁻⁴ and is beyond the scope of this note. The related anomaly, absence of a main branch of the pulmonary artery,⁴⁻⁵ is a different diagnostic and operative consideration.

Practically, the therapy of aplasia of the pulmonary artery is palliative.⁶ However, simple imperforate atretic pulmonic valve should afford a considerably better physiologic, prognostic, and operative opportunity. In pulmonary artery trunk aplasia, supportive care rarely sustains life to a size where thoracotomy and systemic pulmonary shunt can be carried out according to the method for tetralogy of Fallot.⁷ This obviously is not feasible when total aplasia of the pulmonary artery exists and the only collateral circulation to the lung is by means of the bronchial arteries, as clearly shown in Case 1. Schematically these cases include the atretic pulmonary artery, interventricular septal defect, and overdeveloped bronchial arteries (figure 6).

The truncus arteriosus problems have been neatly classified by Anderson and associates⁸ as follows:

- A. True truncus arteriosus (with subgroups)
- B. "Pseudotruncus"

Type 1. Solitary aortic trunk with pulmonary atresia

Type 2. Solitary pulmonic trunk with aortic atresia

Our cases fall under type 1. Cyanotic cases without murmur early and with the presence of a large actively pulsating aorta should arouse suspicion of the defect "pseudotruncus" which may be confirmed by selective angiocardiology.

These 2 cases of pulmonary artery aplasia were encountered in the first 100 patients on whom we elected to perform heart catheterization at Bismarck; of these patients, 75 had congenital heart defects. Only 2 patients with tetralogy of Fallot were catheterized or studied by angiocardiology in our laboratory during this period. We suspect that this unexpected relative frequency of pseudotruncus and infrequency of tetralogy in our experience is due to referral channeling. Perhaps some patients with "clear-

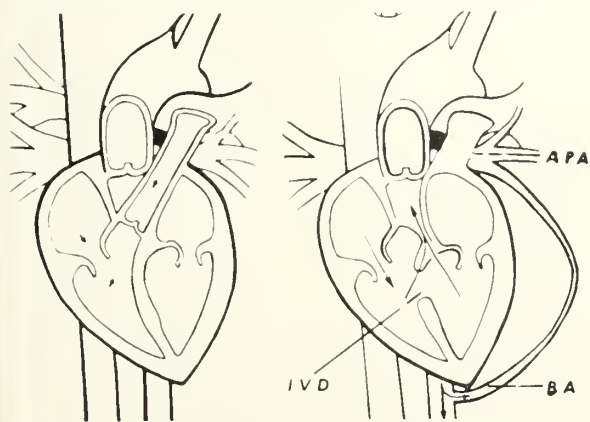


Fig. 6. Normal and atretic pulmonary artery (APA), illustrating interventricular septal defect (IVD) and bronchial artery (BA)

cut" tetralogy of Fallot are referred directly to the open-heart surgical centers.

An occasional case of pulmonary atresia, wherein the pulmonic valve alone is imperforate, is subject to operative correction and hope of long survival.⁹ In this group, salvageable infants make early diagnosis and operation of the failing cyanotic infant an imperative duty. Only a concerted, integrated, and thorough approach, especially capped by selective angiocardiography, serves to diagnose and guide the tenuous surgical approach to pulmonic aplasia.

SUMMARY

Two cases of pulmonary artery aplasia exemplify the problems of exact diagnosis of cyanotic heart disease in infancy. They show that an integrated and concerted study by the cardiologist is essential. The angiocardiographs aid materially in concluding prognosis. The fact that structurally operable defects can be identified (for example, imperforate pulmonic valve) dictates the policy

of early testing in cyanotic infants, despite the usually poor prognosis.

The authors were assisted in this study by the John Hartford Foundation Grant, Bismarck Medical Foundation, and Albert Berg Memorial Fund.

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RESECTION of lung tumors that metastasize from cancer of the female reproductive tract may prolong life and relieve symptoms despite recurrence. Operation is considered if complete removal of the tumor seems possible and if the primary lesion has not recurred or spread. Resection in carefully selected patients is limited to eliminating metastatic disease without making the patient a pulmonary cripple.

D. G. DECKER, J. W. WARREN, O. T. CLAGETT, and D. C. DAHLIN: Treatment of pulmonary tumors metastatic from pelvic cancer. *Am. J. Obst. & Gynec.* 84:192-197, 1962.

PARAFFIN SECTIONS of bone-marrow aspirate are helpful in diagnosing thrombotic thrombopenic purpura when included in the study of unexplained thrombopenic, hemolytic, or other diseases with transient central nervous system disturbances. Aspiration is simple, and bone-marrow specimens may be taken from several sites. One sample provided conclusive evidence in 6 of 8 patients.

E. H. RUFFOLO, G. L. PEASE, and T. COOPER: Thrombotic thrombocytopenic purpura. *Arch. Int. Med.* 110:78-82, 1962.

The In Vitro Cytopathology of Some Common Viruses

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WITH the refinement of methods for the cultivation of mammalian cells *in vitro* has followed the phenomenal growth of modern virology. Within the past decade more facile virus isolation has provided the virologist and clinical investigator with vast etiologic and epidemiologic information. Basic research, cumbersome in the past, has been able to successfully probe the fascinating relationship between the virus and its host cell. Medical science has recently witnessed the evolution of a host of new virus vaccines, both inactivated and attenuated. In turn, the virologist has been confronted with the problem of biologic and physiochemical characterization of viruses, methodologic standardization, and taxonomy.

Cultures of tissue fragments have been used for many years but did not provide an optimal tool for morphologic identification of viruses or precise quantitative research. Employing enzymatic solutions such as trypsin, confluent, nearly homogeneous sheets or monolayers of cells can be cultivated in tubes, Petri dishes or flat-sided bottles.¹ In addition to a host of research advantages, this methodologic advance has often enabled the skilled and experienced virologist to make a presumptive virus identification by observing the morphologic effect of such a microorganism on cultured cells. The morphologic alteration, viewed with the light microscope, has been termed cytopathic effect or "cpe."

The purpose of this paper is to illustrate the *in vitro* morphology of several common and important viruses and in so doing demonstrate the analogy between cytopathic morphology of viruses in cell culture vessels and colony morphology of bacteria on agar Petri dishes.

The continuous culture of cells utilized for this work is of human derivation, liver originally, and is "epithelial" in the parlance of the cell biologist. As to culture characteristics and virus

susceptibility, the cells resemble very closely the well-known HeLa cell. The nourishing fluid, overlaying the cell culture monolayers, consists of a balanced salt solution, yeast cell extract, and bovine serum.

Cell culture pools of strains of the following viruses were prepared: virulent type 1 poliovirus, strain Mahoney; Coxsackie virus, group B, type 5; measles virus, strain Edmonston, HeLa cell-adapted by Dr. John M. Adams; herpes simplex virus, strain Brendes, obtained from ocular washings of a child with keratoconjunctivitis; and vaccinia virus, originally cultivated in embryonated chicken eggs by Lederle Laboratories for the purpose of human vaccination.

Aliquots of the above virus pools were inoculated into cell culture flasks, and at appropriate intervals the cultures were fixed with methyl alcohol and stained with May-Grünwald-Giemsa stain for subsequent photography. The infected

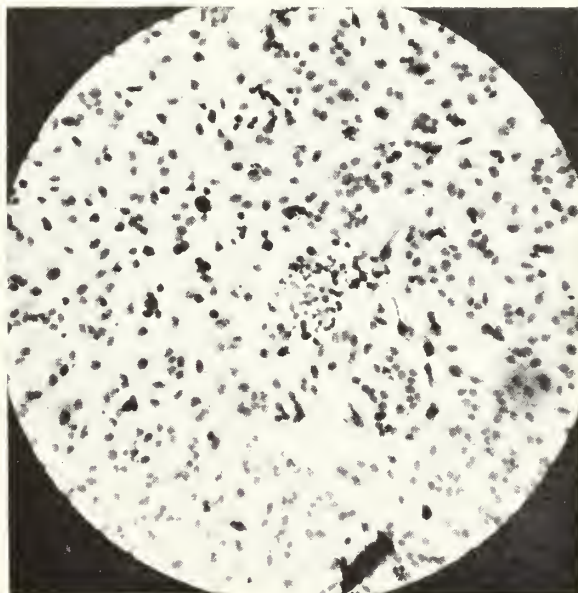


Fig. 1. Poliovirus type 1 in strain Lass cell culture. Focus of cytopathic effect present in the midst of otherwise normal cell monolayer. May-Grünwald-Giemsa stain. $\times 50$

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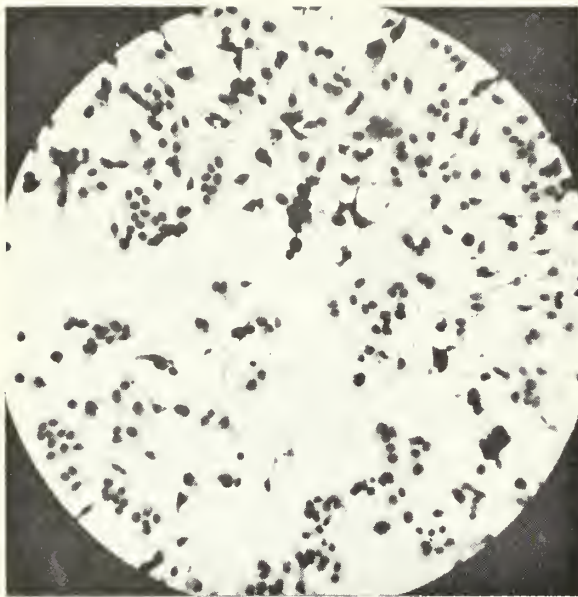


Fig. 2. Coxsackie virus, group B, type 5 in strain Lass cell culture. The residual cell cytopathology may be seen in the upper central area of the field. The dissolution of much of the monolayer is quite apparent. May-Grünwald-Giemsa stain. $\times 50$

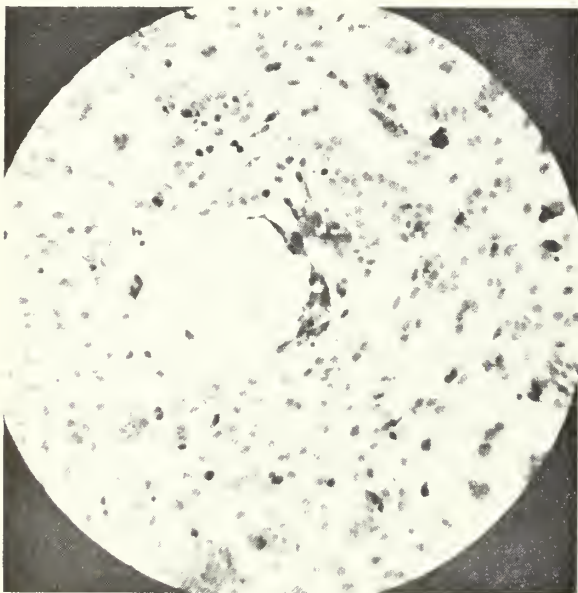


Fig. 3. Measles virus in strain Lass cell culture. The syncytium of multinucleated giant cells has already partially retracted from the glass surface of the culture vessel. May-Grünwald-Giemsa stain. $\times 50$

cell cultures were stained in order to obtain better photographic definition.

The photographic magnification is essentially equivalent to the magnification employed in a virus laboratory using a standard light microscope, approximately $50\times$ or low power.

Infected cultures were photographed at in-

tervals suitable to depict a cytopathic focus in the midst of an otherwise normal field of cultured cells.

Figure 1 illustrates a focus of cells infected by type 1 poliovirus. The area of fusiform, small, almost bullet-shaped cells represents a very early cytopathic change. Within forty-eight to seventy-two hours the majority of cells are usually similarly afflicted and separate from the glass surface of the culture vessel into the overlaying fluids. Such an *in vitro* observation of progression is exemplary of a virus that rapidly invades a cell, capturing the metabolic machinery of the cell in order to direct the replication of new viral particles, then destroys the cell, thus liberating the many viral particles into the overlaying fluids. The newly made viral particles proceed to infect neighboring cells in similar fashion.

The cytopathic morphology of Coxsackie virus, group B, type 5, although one of the enterovirus family, is quite distinct from that of poliovirus type 1. As seen in figure 2, the cells in the cytopathic focus are round, dark, and larger than those observed in figure 1. The infected cells in this photograph resemble a small cluster of grapes. The cytolytic effect of this virus is apparent, as so few cells remain in the field. True of all enteroviruses (polio, Coxsackie, and ECHO viruses), cytopathic alteration of the entire cell monolayer usually occurs rapidly. Such a cultural characteristic may be helpful in establishing a tentative "family" classification of a virus isolate; that is, enterovirus versus adenovirus or herpes virus.

A most fascinating type of cytopathic effect is that of the syncytial variety. The syncytia are thought to occur by the recruitment of infected cells into a single giant cell formed by dissolution of individual cell walls.² They may develop upon inoculation of cell cultures with mumps virus,³ para-influenza viruses,⁴ respiratory syncytial virus,⁵ and measles virus.⁶ The *in vitro* cytopathic morphology of measles virus (figure 3) is in many respects quite similar to the multinucleated giant cells which histopathologically characterize measles infection in man.⁷ In addition to the syncytial changes considerable retraction from the glass surface of the cultural vessels may also be seen.

Figure 4 illustrates the *in vitro* cellular changes observed with herpes simplex virus. The cytopathic focus consists of large, round, balloon-shaped, infected cells which are surrounded by normal cells. Over a period of days additional contiguous foci (daughter foci) of infected cells slowly evolve.

In some instances a syncytial alteration, with

multinucleated giant cells, may represent the *in vitro* cytopathic morphology of herpes virus rather than the proliferative type seen in figure 4.⁸ It is interesting to note that the syncytial form of *in vitro* cytopathology closely resembles the multinucleated giant cells found in the bed of cutaneous herpetic vesicles. Regardless whether proliferative or syncytial cellular change occurs *in vitro*, infected cells usually exhibit, when fixed and stained properly, the type A eosinophilic intranuclear inclusion observed in biopsy or necropsy specimens.

Herpes simplex virus disseminates to neighboring cells in great part by way of intercellular bridges; this is in distinct contrast to poliovirus which, as cited before, is quickly liberated into the overlaying fluid.⁹⁻¹⁰ Thus the *in vitro* infectious process of herpes simplex virus is a slow cell-to-cell phenomenon. The means of virus dissemination is possibly much the same *in vivo* as it is *in vitro*.¹¹

The cultural effects of vaccinia virus resemble superficially those of herpes virus. As depicted in figure 5 the center of the cytopathic focus is almost entirely devoid of cells while the periphery is lined by large, balloon-shaped, conglomerate cells. With higher microscopic resolution, some of these large cells may be seen to be multinucleated. Because of the distinct nummular characteristic of the cytopathic focus, in addition to the loss of cells from the central area, the *in vitro* cytopathology of vaccinia virus differs somewhat from that of herpes virus. For the same reason, distinction can be made from other viruses that produce multinucleated giant cells *in vitro*, such as measles virus and mumps virus. As with herpes virus, the evolution of cellular alteration is relatively slow, and cell-to-cell transmission of vaccinia virus seems to be a major mode of *in vitro* infection.¹²

The distinct cytopathic foci or "plaques," of particular note when the cultures are stained forty-eight to seventy-two hours after inoculation, enable one to quantitate the virus quite accurately by counting the plaques (see figure 6).¹³ Such a technic is very similar to quantitating *Escherichia coli* in a urine specimen by colony counts on an agar Petri dish.

Despite rapid growth in the past ten to fifteen years the discipline of virology is still in the throes of taxonomic struggle. New viruses are being isolated in abundance. Classification of virus groups or families is constantly undergoing revision. Complete standardization of cell cultures, nutritional media, and general methods is yet to be realized among diagnostic and research laboratories.

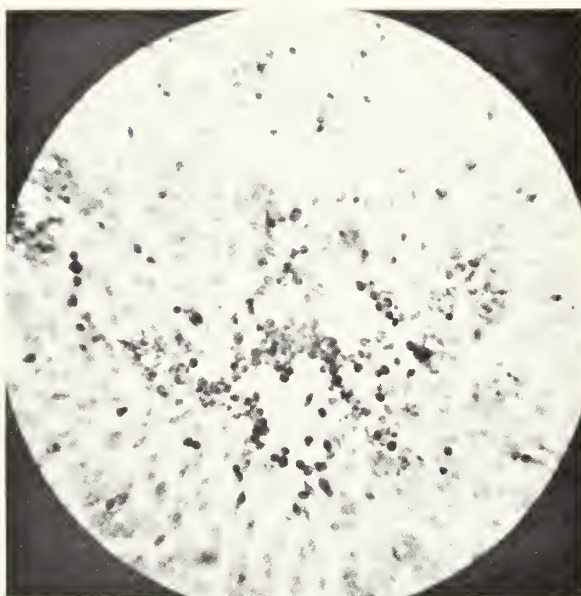


Fig. 4. Herpes simplex virus in strain Lass cell culture. The proliferative type of cytopathic effect can be seen with large, round, dark-staining cells in clusters constituting the infected focus. May-Grünwald-Giemsa stain. $\times 50$

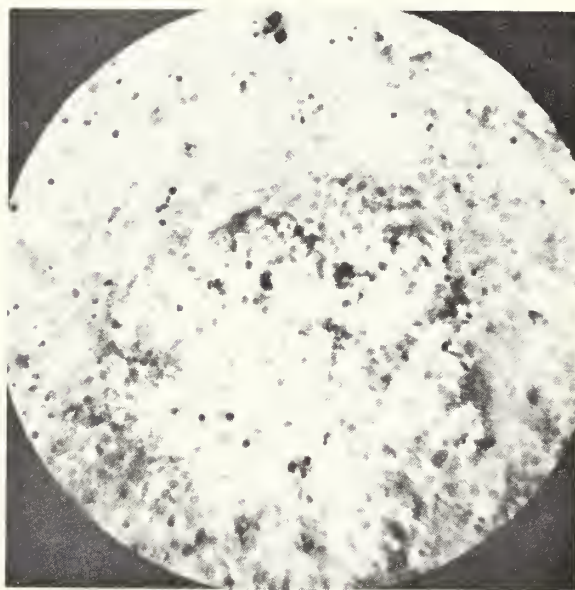


Fig. 5. Vaccinia virus in strain Lass cell culture. The plaque focus is characterized by central cell lysis surrounded by large, ballooning, conglomerate, infected cells. May-Grünwald-Giemsa stain. $\times 50$

Such problems have, in general, been resolved for the bacteriologist. Classification of bacteria is settled and stable. The composition of media for agar plates used in diagnostic bacteriology laboratories is well standardized. From such firm foundations can spring valid morphologic observations and subsequent presumptive bacte-

rial identification. Additional steps should be taken, of course, in all laboratories to more specifically identify or verify a bacterial isolate.

When taxonomic adjustment and methodologic standardization evolve, the experienced virologist may be able to make a presumptive identification of a virus isolate by its cytopathic morphology in a cell culture tube, much as does the bacteriologist observing colony morphology on a blood agar plate. Definitive and final identification must follow whether by *in vitro* neutralization tests with specific antisera or by use of the rapidly expanding fluorescent antibody technic.

At present, viral isolation and diagnostic service is still slow when compared with bacteriologic diagnosis. Laboratory services are often distant, being tendered by a centralized facility such as a state health department. Appropriate and intelligent use of these laboratory services can supply the physician with endemic information concerning viral agents prevalent in the community as well as accompanying patterns of illness. Currently such information can be of immense aid in establishing the most likely viral diagnosis of the individual case. When effective virucidal or virustatic agents become available, considering that certain viral infections demand a chemotherapeutic approach, the need to provide rapid, etiologic diagnosis by specific virus isolation will be at hand. This need may best be satisfied by many smaller virus laboratories located in private and teaching hospitals providing infectious disease services. It would seem most likely that as the demand for prompt and facile virus detection work increases, the necessary basic taxonomy and methodologic standardization will be available. Then viral cytopathic morphology in cell culture vessels may become as useful to the clinician and laboratory diagnostician as is bacterial colony morphology on the agar Petri dish.

SUMMARY

The cytopathic effect of several viruses may be demonstrated by utilizing mammalian cells in continuous culture. The cytopathic morphology is such that for some agents a presumptive identification may be made prior to the final identification by standard neutralization tests.

Human epithelial cells were infected with poliovirus type 1, Coxsackie virus, group B, type 5, measles virus, herpes simplex virus, and vaccinia virus. May-Grünwald-Giemsa stain was used to obtain better photographic representation of the cytopathic morphology as it might be observed unstained in the laboratory.

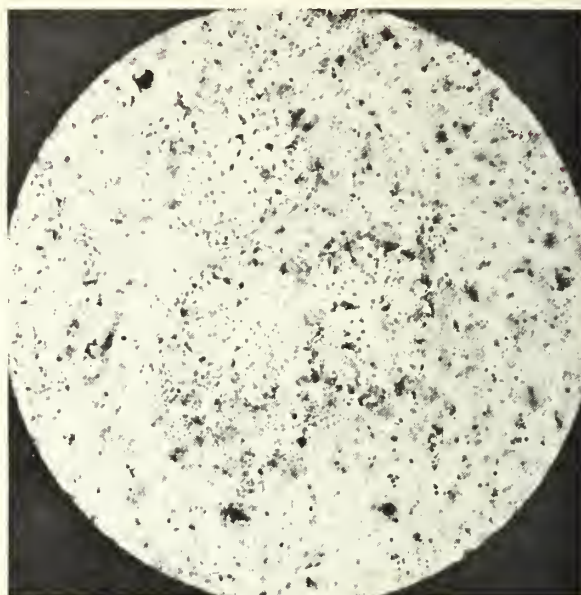


Fig. 6. Vaccinia virus in strain Lass cell culture. With lower magnification, a distinct single plaque focus may be seen at the top of the field and 2 adjoining daughter foci in the central portion. May-Grünwald-Giemsa, $\times 20$

Cytopathic morphology of viruses in cell culture can thus be as helpful as colony morphology on a blood agar plate.

This paper was presented in substantial part at the Fall meeting of the Northwestern Pediatric Society, Bayport, Minnesota, 1961.

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A Multiphasic Screening Project on the Pine Ridge Indian Reservation

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THE DIVISION OF INDIAN HEALTH of the United States Public Health Service provides medical care and public health services to the 7,500 or more Oglala Sioux Indians living on the Pine Ridge Indian Reservation located in the southwest corner of South Dakota.

The people of this reservation have been living under economically depressed conditions since they gradually adopted a money economy. A typical family of 5 lives in a one-room caulked log or frame house, without adequate water or sewage facilities within a reasonable distance of the home. Many larger families live in similar small dwellings.

There is reason to believe that social standards have deteriorated in recent years, with loss of many traditional values and only superficial acceptance of western customs. However, the majority of Indian people can read and write and do understand, although they may not believe, some of the precepts of modern medical care.

Major public health problems on the reservation include acute respiratory illnesses, gastroenteritis, tuberculosis, and trauma. The infant mortality rate (average 1957-1959) was 90 per 100,000 population. This compares with an infant mortality rate of 54 deaths for all Indians on reservations in 24 states and 27 deaths per 100,000 population for the United States as a whole.

Although information is limited, diabetes mellitus seems to be a frequent, but usually mild, disease of older persons. In the 1959 fiscal year, diabetes mellitus was the major diagnosis of 25 or 1.7 per cent of patients discharged from Pine Ridge Indian Hospital. Of these patients, 21, or 84 per cent, were over 45 years of age; most of them were hospitalized for circulatory difficulties rather than diabetes control. During the 1959 calendar year, there were 4 deaths attribut-

able to diabetes, for a mortality rate of 53 per 100,000 population.

Reported cases of syphilis in reservation residents during 1957, 1958, and 1959 totaled 21, 22, and 9 cases, respectively. In these same years there were 27, 65, and 66 cases of gonorrhea. A sizeable number of cases of venereal disease occurred in the 15- to 24-year age group.

METHOD

The Sun Dance is an Indian ceremonial held every summer at Pine Ridge. In years past, about 4,000 persons, mostly Oglala Sioux Indians, attended for the three- to four-day festivities. In addition to the local people, many members of other tribes and a small number of non-Indians attend.

Cooperatively, the local Public Health Service Indian Hospital, the Division of Special Health Services, the Venereal Disease Branch of the Public Health Service Regional Office, the Nebraska and South Dakota State Health Departments, Oglala Sioux Tribal Council, and the Lakota Health Committee planned and carried out the "Sun Dance Health Project" during August 1960.

The project entailed multiphasic screening in which persons were invited to have their blood tested for specific purposes. The first phase of the procedure was conducted in a tent at the Sun Dance grounds. Venous blood in amounts of 5 to 7 ml. was withdrawn into Sheppard visibility vial blood testing tubes containing 50 mg. of sodium fluoride and 5 mg. of thymol as anticoagulant. Each blood specimen was tested on the new Hewson Clinotron at the site. Specimens were then taken to the laboratory at the hospital where rapid plasma reagin (RPR) tests, microhematocrits, blood group, and Rh factor determinations were carried out. Volunteers assisted with various phases of the program. Participants were notified of results of the tests within hours or the next morning, and suspects were referred to the hospital for further instructions, evaluation, and treatment. A hospital

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TABLE 1
PARTICIPANTS IN THE SUN DANCE HEALTH SURVEY BY AGE, SEX, AND RESERVATION STATUS
PINE RIDGE RESERVATION, AUGUST 1960

Age	Pine Ridge Indians		Other Indians		Non-Indians		Total		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
less-15	16	36	1	6	0	3	17	45	62
15-24	92	135	16	19	7	2	115	156	271
25-34	38	33	3	5	5	4	46	42	88
35-44	18	36	6	6	2	1	26	43	69
45-54	22	27	3	6	4	6	29	39	68
55-64	21	24	2	6	5	3	28	33	61
65+	25	13	1	2	2	0	28	15	43
Unknown	0	0	1	0	0	0	1	0	1
Subtotal	232	304	33	50	25	19	290	373	
Total		536		83		44			663

vehicle was used for shuttle service between the Sun Dance grounds and the hospital and transported specimens, reports, and suspects.

At the hospital, the presence of records for the majority of suspects facilitated follow-up. Persons in whom syphilis was found were treated at the hospital, and patients with early infectious syphilis were interviewed regarding sexual contacts. Contact investigations were subsequently carried out. Diabetes suspects were interviewed and new suspects were given appointments for blood glucose and urinalysis determinations. Participants were given cards reporting results of blood grouping and Rh determinations. The results of the hematocrit determinations were technically unsatisfactory so they will not be included.

Agglutination reactions for brucellosis and leptospirosis were carried out by the laboratory of the Nebraska State Health Department on all specimens with sufficient serum remaining after the other tests were completed.

RESULTS

Although the 1960 Sun Dance was rather sparsely attended, 663 of the estimated 2,000 persons at the festivities participated in the survey. Table 1 shows the distribution of these persons by age, sex, and reservation status.

Approximately 80 per cent of the participants were residents of the Pine Ridge Reservation. The greatest degree of participation was by older teenagers and young adults; females took part more than males in most age groups.

DIABETES

Table 2 shows the distribution of positive reactors to diabetes screening in which the Clinitron screened at a blood glucose level of 160 mg. per 100 ml. Inasmuch as no positive reactors were found among the small non-Indian and male "other Indian" groups, these are not included. Although the apparent incidence is higher among "other Indians" than among Pine Ridge Reservation Indians, this difference is not satis-

TABLE 2
POSITIVE CLINITRON REACTORS AND DIABETICS BY AGE AND SEX
PINE RIDGE RESERVATION, AUGUST 1960

Age	Positive reactors		New cases		Cases of Diabetes Previously known		Incomplete	
	Male	Female	Male	Female	Male	Female	Male	Female
15 or less	—	1	—	—	—	—	—	1
15-24	—	—	—	—	—	—	—	—
25-34	—	—	—	—	—	—	—	—
35-44	—	—	—	—	—	—	—	—
45-54	1	4	1	3	—	1	—	—
55-64	3	3	1	1	2	2	—	—
65+	—	2	—	—	—	1	—	1
Subtotal	4	10	2	4	2	4	—	2
Total		14		6		6		2

tially significant, and therefore both Indian groups are consolidated in the table.

Of the 14 positive reactors, 6 were found to be new cases, 6 old cases, and 2 have been lost to follow-ups. Of the 14 positive reactors, 13 were over 45 years of age. Therefore, of 152 Indian people tested in the 45 and above age group, 13 or 8.6 were positive. This is in marked contrast to the 1 positive reactor among 383 Indian people under the age of 45.

SYPHILIS

Table 3 shows the positive reactors to the rapid plasma reagin test and the diagnosed cases of syphilis. Again the non-Indian group has been eliminated because of absence of positive reactions in that group. Of 24 positive reactors, 10 were treated, 12 had had previous adequate treatment, and 2 were found not to be infected with syphilis. Of 10 treated patients, 3 had early latent syphilis and 5 were treated for late latent disease; 1 received epidemiologic treatment, and 1 was returned to treatment when the previous therapy was judged inadequate. Although a large segment of females and young people were among the group tested, the number of cases discovered in the young population was relatively small. In fact, the percentage of positive reactors was greater in older than in younger persons.

The 3 patients with "infectious" syphilis were young (15 to 34 years of age). At interview, these 3 patients indicated a total of 24 sex contacts. In addition, the "eluster" technique was employed which produced 11 suspects and six associates. Of the 24 contacts, 5 were found infected with syphilis, 1 had gonorrhea, and 3 were given epidemiologic treatment. The other 15 contacts were not infected with venereal disease.

Of the 5 contacts found to be infected with syphilis, 2 recently had had adequate treatment for the disease, 2 were returned to treatment on the premise that previous treatment had been inadequate, and 1 was brought to treatment for primary syphilis. Follow-up of the contacts of this patient led to an infectious "chain" of syphilis which involved 6 additional persons who resided off the Pine Ridge Indian Reservation. Of the 11 suspects obtained from the patients originally uncovered by the screening tests, 10 were not infected with syphilis. One suspect, a child recently born to one of the infected patients, was given epidemiologic treatment for syphilis.

Of the 6 associates, 1 was found to be a new case of late latent syphilis and the remaining 5 were not infected.

As a result of the survey, therefore, 25 individuals received treatment for venereal infections.

BRUCELLOSIS

The results of the screening tests for brucellosis were as follows: 25 of the specimens reacted to some extent; only 2 were as high as 1:80. These results indicate that, although there may be some brucellosis or possibly tularemia among the group, the low titers indicate low incidence of the infections.

LEPTOSPIROSIS

Of the 623 specimens which were screened for leptospirosis, 1 was positive in a dilution of 1:320 and 2 others were equivocal. The positive patient is a 40-year-old woman who has had 6 pregnancies, of which 3 ended in spontaneous abortions. It is possible that she may have leptospirosis although the diagnosis has not yet been confirmed. At any rate the incidence of

TABLE 3
RAPID PLASMA REAGIN REACTORS AND CASES OF SYPHILIS
PINE RIDGE RESERVATION, AUGUST 1960

Age	Positive reactors		Syphilis cases newly treated		Syphilis cases Adequate previous treatment		Not infected	
	Male	Female	Male	Female	Male	Female	Male	Female
Less-15	—	—	—	—	—	—	—	—
15-24	—	2	—	1	—	1	—	—
25-34	3	2	1	2	1	—	1	—
35-44	2	2	—	—	2	2	—	—
45-54	—	3	—	2	—	1	—	—
55-64	4	3	1	1	3	1	—	1
65+	2	1	1	1	1	—	—	—
Subtotal	11	13	3	7	7	5	1	1
Total	24		10		12		2	

leptospirosis in the population tested is relatively small.

BLOOD GROUPS AND RH FACTORS

Of 618 Indian people tested, only 6, or 1 per cent, were Rh negative. This is in contrast to 13.5 per cent among the white population and 8.1 per cent among the Negro population, according to Wintrobe. Regarding blood groups of all of the Indian persons tested, 61 per cent were O, 35 per cent were A, 3.2 per cent were B, and 0.6 per cent were AB. These percentages compare with 41, 41, 11.6 and 7.5 per cent respectively, for white persons, according to Wintrobe. There appears to be no distinction according to sex, age, or Pine Ridge residency as compared with "other Indian" people tested.

SUMMARY

A multiphasic screening project was carried out during the Sun Dance festivities on the Pine Ridge Indian Reservation in August 1960. Of approximately 2,000 individuals in attendance, 663 (30 per cent) participated in the survey. The project was the result of the cooperative efforts of the local Public Health Service Indian Hospital, the Division of Special Health Services, the Venereal Disease Branch of the Public Health Service Regional Office, the Nebraska and South Dakota state health departments, the Oglala Sioux Tribal Council, and the Lakota Health Committee of the Oglala Sioux Tribe.

Screening tests were carried out for diabetes, syphilis, leptospirosis, and brucellosis, and determinations of blood group and Rh were made.

Of 152 Indian people tested for diabetes in the 45-and-over age group, 13, or 8.6 per cent were positive. Of these, all but 1 were found to have diabetes; 6 were new cases.

Syphilis screening revealed 24 positive reactors; of these, 10 were treated for syphilis, 12 had had syphilis but had previously been adequately treated, and 2 were found not to be infected with syphilis. From 3 newly discovered early latent cases of syphilis, contact investigation resulted in 25 individuals being treated for venereal diseases.

Rh studies and blood grouping revealed that only 1 per cent of the Indian persons tested were Rh negative; 61 per cent were blood group O, 35 per cent blood group A, and very few were B or AB.

The survey was considered a very definite success and well worth the time, cooperative effort, and materials expended on it. In addition to the cases of diabetes and syphilis which were brought to treatment, a considerable amount of new medical knowledge was uncovered. Moreover, the results of the blood typing provided information available for the local "walking blood bank" of Pine Ridge Indian Hospital. The survey provided the Indian people who participated with a health service they would otherwise not have had at their disposal.

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SYMPTOMATIC abdominal aortic aneurysms and such aneurysms without symptoms and no associated cardiovascular disease should be treated surgically. Patients with small asymptomatic aneurysms and associated cardiovascular disease probably should be kept under observation until symptoms due to aneurysm appear or signs are noted of expansion of the aneurysm.

L. J. SCHATZ, J. F. FAIRBAIN II, and J. L. JUERGENS. Abdominal aortic aneurysms: a reappraisal. *Circulation* 26:200-205, 1962.

Transactions of the North Dakota State Medical Association

SEVENTY-FIFTH ANNUAL MEETING

Bismarck, North Dakota, June 2, 3, 4 and 5, 1962

(Continued from the November Issue)

REPORTS OF SPECIAL COMMITTEES

Committee on Mental Health

The committee met once, with a good turnout. Throughout the year, members have been working on the advisory board to the State Board of Administration, and with the Mental Health Authority.

On March 17, 1962, we formulated proposals we hope will be carried through. We have approved a program of mailing educational matter on mental health to members of the association who are interested. After 2 or 3 mailings, a card will be sent asking the doctor to signify if he wishes to continue receiving it. We hope for better understanding of mental health and what the family physician can do for this program in the state. This program will be a joint effort of the Committee on Mental Health of the State Medical Association and the Mental Health Committee of the North Dakota chapter of the Academy of General Practice.

The committee moved to support enabling legislation which would allow the formation of community mental health service units in political subdivisions during the 1963 legislative session. We would use Senate Bill 47 from the 1961 session as a guide. We hope the House of Delegates will see fit to back this legislation. The bill reads as follows:

"Senate Bill No. 47—For an Act to authorize the establishment of community mental health service units, to provide for their administration and for state aid and assistance from the state health department, and to authorize a mill levy of not to exceed three-quarters of one mill for such purpose.

Be it enacted by the Legislative Assembly of the State of North Dakota:

Section 1. Establishment of Community Mental Health Service Units. Any city, village, county, health district, or any combination thereof, or private nonprofit corporation, may establish and maintain community mental health service units and may establish clinics and staff the same with persons specially trained in psychiatric and related fields. Such programs and clinics shall be administered by the board of directors of the community mental health service unit when undertaken by political subdivisions and by the nonprofit corporation in such manner as is consistent with state law and rules and regulations of the state health department.

Section 2. State Aid—Application—Local Support. Cities, villages, counties, health districts, or any combination thereof, and private nonprofit corporations may apply to the state health department for assistance in establishing and maintaining community mental health service units. In the case of a private nonprofit corporation a contract between the state health department and the corporation shall be entered into for state aid and for the provision of mental health services by such corporation, which contract shall be upon such terms as the State Health Department shall prescribe. The unit or corporation requesting state aid shall submit to the State Health Department not later than July First of each year the proposed budget for the following year, plus detailed plans with regard to the extent of services and programs to be undertaken. Before the department allocates any funds

to any unit maintaining or establishing community mental health services, the proposed budget and detailed plans shall be approved by the department. During July of each year the State Health Department shall allocate funds, to the extent available, to the various units in accordance with approved budgets and plans. The Department shall have authority to reallocate unencumbered funds that have been allocated and may withdraw unencumbered funds if the services and programs of the community mental health service unit do not correspond to the approved budget and plans forwarded to the health department.

State support to any community mental health service unit shall not exceed forty percent of such unit's total expenditure for salaries, contract facilities and services, maintenance and service costs, expenses of the board of directors of the unit, and other expenses authorized by the state health department. No reimbursement from moneys appropriated to the state health department by the legislative assembly shall be authorized for any capital expenditures.

A community mental health service unit comprising only one political subdivision may receive aid from such political subdivision to the extent that its governing body agrees to participate. If a community mental health service unit comprises more than one political subdivision, the unit shall receive aid from the political subdivisions in proportion to the assessed valuation of each political subdivision or in such manner as their governing bodies shall agree. A private nonprofit corporation may receive aid from any political subdivision on a contract basis, entered into between the officers of the corporation and the governing body of the political subdivision, for services to be rendered to the political subdivision and its residents. However, any aid given to a community mental health service unit or nonprofit corporation shall only be made from the general fund of such political subdivision unless an additional mill levy, not to exceed three-quarters of one mill, is authorized and approved by a majority of the electors of the political subdivision voting on such a mill levy increase at any special or regular election. The mill levy provided herein shall be over and above any mill levy limitations provided by law.

Section 3. Board of Directors—Appointment—Term. Each community mental health service unit shall be governed by and under the general supervision of a board of directors. The board of directors shall be appointed by the governing body of the political subdivision which comprises such unit, and if more than one political subdivision comprises such unit then appointed by the governing bodies of each such political subdivision meeting jointly. The board of directors shall not exceed nine members, but may be less in the discretion of such governing bodies. The term of office of the board members shall be three years, staggered so that the term of office of an equal number of the board members, if possible, expires each year. Vacancies occurring on the board for other than the expiration of a term shall be filled in the same manner as original appointments, except that appointments shall be made only for the unexpired term. No compensation shall be allowed the board members, but they shall be allowed the same mileage and expenses as is allowed state officials. The board shall elect a chairman from their membership and such other officers as the board deems necessary. All members of each board of directors shall be residents of the area served by the community mental health service unit and such membership shall represent as nearly as possible local health departments, medical societies, county welfare boards, hospital boards, and other lay and professional organizations and people.

Section 4. Powers and Duties of Board—Administration.) The following powers and duties shall be performed by the board of directors of the community mental health service unit:

1. Determine, review, and evaluate services and programs provided by the unit and make periodic reports thereon to the state health department, together with any recommendations the board may have for improvement in services, programs or facilities;
2. Recruit and promote local financing from private and public sources;
3. Promote and arrange for cooperation and working agreements with other social service agencies, public and private, and with individuals and organizations in the educational field and judicial branch of government;
4. Determine the budgets and submit them to the governing bodies of the political subdivisions concerned for their approval and prepare detailed plans for services and programs of the unit for the forthcoming year; and
5. Perform any other act necessary to properly administer the community mental health service unit. The board may employ such professional personnel as may be necessary to properly staff the community mental health service unit and may in its discretion employ such administrative personnel as may be necessary to assist them in the performance of their duties, including an administrator. The board may delegate to the administrator such of its powers and duties as the board deems necessary and desirable."

There was discussion of a state children's psychiatric unit. This committee two years ago stated it would try to come up with some answers on a children's psychiatric hospital. It was agreed that a pilot program be considered for the State Hospital in Jamestown for the intervening two to four years. It was the general opinion that this probably would work out better and would give us a better idea of exactly what and how much was needed, and how it would work out.

Dr. Schmidhofer, superintendent of the State Hospital, said he would try to implement a program in the near future.

The committee expressed a desire for sponsoring seminars for physicians interested in the general subject area of the cooperative management of psychiatric patients. This program will be formulated through the summer and should be in action this fall. We will try to cooperate with the Academy of General Practice and see if we can obtain category 1 credit for attendants. Dr. Samuelson offered to help set up this program. His offer was accepted gratefully.

Dr. Rand of the State School of Grafton requested that we advise physicians that it would be a good idea if children with mongolism be kept in their communities a little longer before sending them to the state school.

The state programs were discussed, and the committee was pleased with the progress being made in all areas. We will need the cooperation of all members in the coming year to improve our state mental health program, and we know that we will get that backing.

K. G. VANDERSON, M.D., Chairman

Committee on Cancer

The committee had 2 formal meetings, May 10 at Fargo in conjunction with the annual meeting, and December 10 at Fargo with the Interim Meeting of the council.

In addition to usual business, cancer quackery was discussed thoroughly. Much publicity has been given the cancer quack during 1961, and there appears to be a national effort to eradicate this low form of human being by means of legislation in the various states. Secretary Ribicoff of HEW and Leonard Larson, president of the A.M.A., temporarily buried the hatchet and had their

picture taken together in front of a backdrop which depicted the evils of cancer quackery. Four states, California, Nevada, Colorado, and Kentucky, have passed anti-quackery legislation. Copies of these bills were reviewed. The committee will decide upon the proper type of legislation at our state meeting in June. Our efforts will be directed to presenting a good anti-quackery bill at the next legislative session.

The North Dakota division of the American Cancer Society remains active in all branches of cancer control. Dr. John Gillam, chairman of the executive committee, and chairman of the Professional Education Committee, will present the annual Cancer Caravan later this season at Fargo, Grand Forks, Minot, and Bismarck. The speaker will be Dr. George Moore from Roswell Park Memorial Hospital in Buffalo, New York. Roswell Memorial is one of the better cancer detection and treatment centers in the United States. I visited this hospital in 1957 and received a most favorable impression. Dr. Moore will present a symposium on "Chemotherapy in the Treatment of Cancer." I have been fortunate to hear Dr. Moore speak on two occasions on this subject and I know of few better qualified in the field. I urge your attendance. The dates will be announced later by the North Dakota division of the American Cancer Society.

Dr. O. W. Johnson of Rugby is the current president of the board of the North Dakota division of the American Cancer Society and medical delegate to the national convention. He is contributing his efforts in building up strength in the state in the cancer organization. We hear he has received an invitation from Reykjavik, Iceland, to present a cancer symposium this summer.

Dr. C. Hamre, professor of anatomy at the University Medical School in Grand Forks, is a member of the Institutional Grants Committee of the American Cancer Society. This position takes him to various cancer centers and institutions throughout the United States. His work consists of inspection and approving or disapproving cancer grants to these institutions.

Dr. Cornatzer, professor of biochemistry at the University of North Dakota Medical School, has received an additional grant from the American Cancer Society to continue his research in mammary tumors. We hope that those in advantageous positions will expend all efforts in promoting grants-in-aid to the staff of our medical school.

Your chairman attended several cancer sessions during the past year, including the regional meeting of the American Cancer Society in Billings, Montana, the interim sessions of the American Cancer Society in Seattle, Washington, the North Dakota division of the American Cancer Society meeting in Fargo, the annual meeting of the American Cancer Society in New York, a Research Grants Committee meeting in New York, and the meeting of the board of directors of the American Cancer Society in New York.

The American Cancer Society is contributing approximately \$10 million during the coming year for grants-in-aid for cancer research. The National Cancer Institute is pouring in at least \$50 million of federal funds in pursuit of this same project. There is no question but we are on the verge of a breakthrough in the discovery of the cause of cancer. Much information has been presented during the past five years in cancer therapy. This will continue with the help of the American public. More information on cancer research will be presented to the public from the Eighth Annual International Cancer Congress in Moscow July 22, 1962. Your chairman received an invitation to attend this session, but several conflicts prevented acceptance. I will, however, re-

port to you later on any news of importance that we hear from this session.

Most of the doctors in North Dakota have received invitations to appear on the speakers' bureau in the various counties in the state. You will receive adequate literature from our state office, and only a few minutes are needed for preparation. We hope you will assist your county commander by contributing your time and talents to promote the activities of your county cancer unit.

CARROLL M. LUND, M.D., Chairman

Committee on Veterans Medical Service

No special problems have been presented to this committee. Consequently, it has not met during the past year, and it is making no recommendations.

ROBERT F. NUSSLE, M.D., Chairman

Committee on Maternal and Child Welfare

The committee met on March 3, 1962, at the Fargo Clinic, Fargo, and recommends the following:

1. As soon as funds are available, we recommend that the educational series called "Pierre the Pelican" be purchased from the Louisiana health authorities and given to parents with their firstborn. This is an educational series of 12 monthly leaflets.

2. We recommend that all hospitals do the blotter screening test for phenylketonuria. This method was devised by Robert Guthrie, M.D., Ph.D., research associate professor of pediatrics, Children's Hospital, Buffalo, New York. The laboratory work would be sent to Grand Forks, and the laboratory division of the North Dakota State Department of Health would do the tests. This procedure would be of no cost to physician, hospital, or laboratory. It was also the unanimous suggestion of the committee that each participating physician do a diaper test at the six-week checkup by any means he desires.

3. We recommend that all hospitals not doing perinatal studies use the outline supplied by the Medical Research Foundation.

4. Since the Maternal Mortality Review Board is an investigating board, and the Maternal and Child Welfare Committee an advisory group, it was recommended that the Maternal and Child Welfare Committee, on information supplied by the Maternal Mortality Review Board, give pertinent information on maternal deaths to the physicians of the state. The Maternal Mortality Review Committee has given sanction for any proposed action of this committee. We further recommend that

1. The investigator of each maternal death return to the physician and inform him of the decision of the Maternal Mortality Review Board. The honorarium and expenses will be paid by the MCH division of the North Dakota State Department of Health.
2. The investigator will present a review of the cases at the district medical meetings every two or three years. This will be done by an investigator who did not appear in that area. Again, the State Department of Health would assume honorarium and expense.
3. A résumé of the highlights of the maternal death investigation in North Dakota would be written for publication in the near future and published in the JOURNAL-LANCET.

ROBERT E. LUCY, M.D., Chairman

Committee on Diabetes

The Committee on Diabetes, initiated by Dr. Leonard Larson of Bismarck, has continued its primary function to encourage and coordinate annual diabetes detection drives throughout the state under sponsorship of constituent local medical societies. This function is a co-operative effort in support of National Diabetes Week, sponsored in November each year by the Committee on Detection and Education of the American Diabetes Association, Inc. Increasing participation is in evidence among district medical societies throughout the nation. Last year, well over 1,000 societies held individual detection drives.

Only 2 formal diabetes detection drives were held in North Dakota during Diabetes Week 1961 in Grand Forks and Minot. Dr. L. A. Giltner, chairman of the Diabetes Detection Committee for the Fourth District Medical Society, reported that 5,000 Drey-Paks were distributed throughout the public school system and 386 tests were returned. Of this total, 35 positive tests were found in the urine. Adequate follow-up was received on all 35 positives and led to the diagnosis of 8 new cases of diabetes mellitus. Among these was a bona fide case of renal glycosuria with no evidence of diabetes mellitus.

An informal detection drive was carried out by Dr. B. Z. Hordinsky of Drake, who tested over 600 persons from Drake and surrounding communities. Through the sole efforts of Dr. Hordinsky, 4 new cases of diabetes were diagnosed.

The most extensive detection drive took place in Grand Forks and the surrounding community November 12 to 18 under the auspices of the Grand Forks District Medical Society. The Diabetes Detection Committee consisted of Dr. Richard K. Helm, chairman, Drs. William T. Powers, Harold W. Evans, Keith G. Vandergon, and E. A. Haunz. Drs. Powers, Evans and Vandergon were in charge of publicity.

Drey-Pak testing kits were supplied by the American Diabetes Association, and funds to purchase these kits were supplied by the Grand Forks District Medical Society, the United Fund of Grand Forks County, and the North Dakota Public Health Service.

Supporting groups in this project included the Grand Forks Chamber of Commerce, Grand Forks Junior Chamber of Commerce, Sertoma Club, Kiwanis Club, Lions Club, St. Michael's Hospital, Deaconess Hospital and University of North Dakota School of Medicine and School of Nursing. Many local physicians cooperated, as well as local drug stores. Excellent support for publicity was given by radio stations KILO and KNOX and by KNOX-TV. Publicity was begun four to six weeks before Diabetes Week and was conducted in such a manner that maximum public awareness of the program was created by the opening date of the drive.

St. Michael's Hospital served as a central distributing point on November 14, and 35 drivers from various service clubs participated, together with 70 student nurses from the hospital, the University College of Nursing, and Deaconess Hospital. The city was divided into sections, each containing 300 possible points of distribution for the test kits. A description of each section was outlined on a card for each corresponding driver, and approximately 300 test kits were distributed by each functioning unit. In only four and one-half hours this efficient team succeeded in distributing nearly 10,000 kits door-to-door. The TV station video-taped distribution of the kits and later televised it in order to induce people to return their tests. The following day displays

were set up in the lobbies of both hospitals, together with test kits. Several hundred test kits were distributed at drug stores throughout the community. In this manner, about 3,000 more test kits were distributed, bringing the total to 13,000.

Some 3,000 test kits were returned, with 185 found to be positive. Emphasis was placed upon reporting false positives rather than false negatives. There followed the long, arduous task of seeing that each attending physician was properly notified. To date 13 per cent of the positive reactors were found to be new diabetics (24 cases). The results indicated that this highly efficient program not only led to the discovery of a significant number of new diabetic patients, but was an excellent community service and engendered considerable goodwill toward the medical profession, as well as to other functioning groups who cooperated in making this drive a success.

As chairman of the State Committee on Diabetes, I would like particularly to commend Dr. Helm for his untiring efforts in organizing and completing one of the most successful drives in the history of diabetes detection in North Dakota. It is hoped that the success of this drive will serve as a stimulus for more widespread participation in future years, since there are many hidden cases throughout the state awaiting discovery. In conclusion, my sincere thanks to all committee members for their wholehearted cooperation and support throughout the years.

E. A. HAUNZ, M.D., Chairman

Committee on Crippled Children

A meeting of the committee was held at 9:30 a.m. on December 9, 1961, in the Gardner Hotel in Fargo. Present were Chairman Paul Johnson and Drs. C. W. Hogan, A. E. Culmer, D. T. Lindsay, B. A. Mazur, G. M. Hart, J. V. Miles, George Foster and G. W. Toomey. Others present were Dr. E. H. Boerth, Mr. Dale Boehm, Mr. George Michaelson, Mr. Daniel Buchanan and Mr. Orville Hawes.

The chairman's opening remarks were relative to the State School at Grafton, where 23 children with mongolism were staying who, according to the superintendent, belonged in their own communities. Dr. Johnson reported that the Grafton School urged physicians to be more judicious in referring children (especially those with mongolism) to the school because of the ever-increasing case load of young children and babies and facilities not adequate to care for them. A number of the members wanted to know if the Grafton School was discouraging admission of children primarily because of a lack of facilities. Dr. Mazur thought not, pointing out that his experience showed him that those with mongolism who were not destructive should be kept out of Grafton, since they adapted better socially when in their home environments. Dr. Mazur then moved that the committee recommend that physicians be urged to care for these children in their homes, and that the Grafton facilities be used only when absolutely necessary. Dr. Culmer seconded the motion, and it passed unanimously.

As an adjunct to the discussion on Grafton and care of children with mongolism, Drs. Miles, Lindsay and Mazur discussed the use of the PKU test in the detection and early treatment of the disease. Members of the committee agreed that good infant care was essential to preventing the problem. It was moved by Dr. Mazur, and seconded by Dr. Lindsay, that the State Health Department undertake an education program for physi-

cians in the PKU detection program. Unanimous approval was voiced.

Mr. George Michaelson, state representative of the National Foundation, expressed his thanks to the committee for past cooperation, and introduced Mr. Dale Boehm, his area supervisor.

Mr. Boehm explained the National Foundation's reasoning for no longer authorizing payment of physicians' fees by its chapters. He read a letter sent to Dr. E. H. Boerth, president, North Dakota State Medical Association, on August 7, 1961, wherein the Director of Medical Care for the National Foundation, Dr. William S. Clark, told of the foundation's plan to direct its patient aid policies toward the ancillary costs of long-term illnesses, rather than physicians' fees which, he said, were really the lesser economic burden on families and individuals afflicted with long-term catastrophic illnesses.

Mr. Boehm reported on the National Foundation's new policy of directing monies toward research and professional and public education, as well as patient aid, in combatting congenital malformations and arthritis. He told of the program of sending certain polio patients, as well as others, to university clinic centers where they might receive maximum professional skills available, and prove helpful to the universities in terms of teaching and research. Chairman Johnson asked if any persons from North Dakota were being sent to universities for research, teaching or care purposes, and whether the local chapters of the National Foundation were paying for the care of patients other than those with polio. Mr. Michaelson replied that North Dakota efforts were being directed largely toward research and public and professional education, since the supply of available money was limited sharply. Michaelson also stressed the need for local medical advisory committees in North Dakota to help carry out the foundation's program, and to determine need of recipients.

Mr. Orville Hawes of the Easter Seal Society gave each person a copy of his latest annual report and a copy of the physical examination blank being used at Camp Grassick. He called for comments on each of the documents. He said that, to date, he had been unable to implement the plan suggested in 1961 by his predecessor, Mr. William Unti, since he was not completely familiar with it, and had been in the state only a short time. He told of his proposed plan to conduct speech, hearing, and epilepsy clinics throughout the state. A pilot project of meetings with parents of physically and mentally handicapped children is being carried out currently, as well as high school and college career education programs for the recruitment of interested persons into the field of rehabilitation. He said the establishment of hearing clinics was being given serious consideration.

Dr. Foster said that a program of hearing clinics was of questionable value, but Dr. Johnson pointed out that the North Dakota Academy of Ophthalmology and Otolaryngology might be interested in discussing the matter. Johnson said that since epileptic seizures were so dramatic, clinics for detection were not justified.

Reports on CCS were distributed by the chairman, and the problem of paying a per diem stipend to hospitals from CCS funds was discussed. Committee members felt that a uniform rate should be established, since they did not feel that it was equitable for hospitals to charge regular fees for CCS cases when physicians received either a reduced fee or nothing at all. One of the discussants pointed out that hospital costs have risen some 300 per cent in the area of CCS, while doctors' fees have shown a 15 per cent increment over the same period of time. It

was suggested that some method be arrived at for requiring hospitals to submit a detailed accounting sheet to CCS, and that payments made to hospitals be on a pro rata basis. Dr. Miles felt that hospitals should be paid on much the same basis from CCS as they are paid by public assistance. The committee decided to make no formal recommendation on the CCS difficulty with hospitals, but if it were not alleviated or solved soon, the entire issue would be discussed again.

The committee was informed that county welfare boards would be exercising more discretion in the handling of medical welfare recipients after January 1, 1962. Prior to now, the counties as such took no official action other than having the executive secretary of the Welfare Board determine recipients.

PAUL JOHNSON, M.D., Chairman

Committee on Aging and Rehabilitation

Committee make-up has been changed considerably from previous years, with an attempt to have a representative from each district society on the committee.

The committee met in Fargo on December 8, 1961 with 7 members in attendance. It was recommended that each district president appoint a 3-man Committee on Aging and Rehabilitation, and if there were a member of the State Committee on Aging and Rehabilitation in that district, that he be one of the members. The purpose of this committee would be to have a nucleus of informed physicians on the challenges of aging and rehabilitative services available in each district to acquaint member physicians more thoroughly, to be available for public appearances, and to work with district committees.

It was recommended that each district society sponsor at least one program yearly on rehabilitative services available. It is felt by the committee that the directory of rehabilitative services that has been sent to all physicians in the state catalogs services available, but that many physicians in our state are not aware of the services available to them. This would be another reason for the district society committee to act as a source of information and encouragement.

It was recommended that a physiatrist be obtained to work with the rehabilitation unit at Grand Forks to serve as a consultant and to direct physical therapy rehabilitative services in and about the state and be available for consultation at clinics throughout the state.

Dr. J. R. Amos, State Health Officer, advised that two funds were available to our state; one to organize and help subsidize a visiting nurse service, and one to organize and finance a homemaker's service. It was felt that a home nursing service was probably a more crying need at the present. This service could be administered through a voluntary local nursing board or a local health department with the Public Health Service assisting in every way possible, such as furnishing office space or sharing personnel. It was suggested that a pilot program be instituted in the First District Medical Society, with the objectives to be: (1) make nursing home service available to the chronically ill; (2) reduce the cost of hospitalization for chronically ill patients; (3) alleviate hospital bed shortages; (4) decrease the need for more hospital beds; and (5) educate the patient himself.

The patients would be referred to the service by a physician and remain under his care through his instruction to the visiting nurse. The services would be on a pay basis as to the patient's ability to pay, with a pay schedule set up by the administering unit in the First

District Society. This program was presented to the council and received its approval for implementation in the First District Society.

The committee discussed the desirability of giving indigent people going on welfare a prophylactic examination. A preventative medical program appears to be a valuable method of eliminating prolonged medical care. This was assigned to several members of the committee for further study.

The committee concerned itself about instituting progressive hospital care in major hospitals about the state. This has been referred for further study.

Our committee concurred in the necessity of expanding voluntary health insurance coverage for the aged, and commends Blue Shield and Blue Cross for efforts in this area. Our committee concurs that the present system of local control of medical services, using local, county, state, and federal support by way of matching funds, be continued.

Drs. Charles Graham, Ted Harwood, and T. E. Pederson remained members of the State Council to Improve the Health Care of the Aged, representing medicine.

T. E. PEDERSON, M.D., Chairman

Committee on Foreign Trained Physicians

The large number of graduates of foreign medical schools entering the United States continued during the past year. It has been estimated that from 1958 through 1961 about 28,500 of these graduates have been examined by the Educational Council for Foreign Medical Graduates, and of this number about 20,000, or nearly 70 per cent, have been either fully or temporarily certified. (Fully certified is a grade of 75 per cent or over. Temporary is a grade of 70 per cent to 75 per cent.) It is amazing to learn that on an annual basis, the number of foreign graduates fully or temporarily certified by the E.C.F.G. begins to approximate the annual output of graduates of U.S. medical schools. It appears that in a few years there will be a foreign graduate intern for every 2 U.S. graduate interns on duty in hospitals in the U.S. This is a fact to be remembered.

There are 81 examining centers established in foreign countries by the National Board of Medical Examiners, which is acting as a screening agent. About 35 per cent of the applicants who write these examinations in foreign lands obtain a grade of 75 per cent or better, and an additional 23 per cent obtain a grade between 70 per cent and 75 per cent. The magnitude of the interest in obtaining admission to the U.S. is illustrated by the fact that 700 applicants wrote this examination in October 1961 in Manila, Philippine Islands. About half were women. The Philippines sent more physicians to the United States last year (2300) than any other country.

About 38 of the 50 State Medical Boards use the E.C.F.G. examinations as an aid in selecting qualified foreign physicians for admission to their examinations.

During the past year, the North Dakota Board of Medical Examiners examined 7 applicants who were graduates of foreign medical schools. Six passed and 1 failed. During the past 10 years, the North Dakota Board has examined 57 applicants of foreign medical schools, and of this group, 43 were granted a license and 14 failed. (Canadians are not considered foreign graduates). Of the 36 foreign graduates who are practicing in North Dakota today, 16 are in general practice and 20 are in the specialties.

The majority of foreign medical graduates who write

in to the secretary of the North Dakota State Board of Medical Examiners for information regarding licensure in North Dakota are interested in practicing a specialty, if licensed, and are not interested in general practice in a rural area where physicians are needed.

It is unfortunate that some foreign graduates who do not meet the requirements for admission to the North Dakota State Board examinations, as stated in the North Dakota Medical Practice Act (especially relative to an approved internship), are disturbed when the board will not waive these legal requisites. Board members are under oath to uphold the many provisions of the medical practice act and cannot grant special privileges to any physician.

C. J. GLASPEL, M.D., Chairman

Committee on American Medical Education Foundation

Donations to the American Medical Education Foundation fell short of the mark established in 1960, which was our best year. Although the number of participants increases, the size of the donations seems to be diminishing. Considering the country as a whole, over \$1,300,000 was raised for medical schools.

Through the mails you have been advised of the merger of the American Medical Education Foundation, established in 1951 for the purpose of providing financial assistance to medical schools, with the American Medical Research Foundation, established in 1957, and with its principal aim the betterment of public health through scientific and medical research. The title now will be the American Medical Association Education and Research Foundation. It is felt that this combination will provide a sounder basis for future expansion and allow unified direction and control within the framework of a single foundation.

Purposes of AMA-ERF are: (1) to promote the betterment of public health through scientific and medical research; (2) to plan and initiate scientific and medical research activities; (3) to make financial grants-in-aid for research projects; (4) to collect, correlate, evaluate and disseminate in the public interest the results of the scientific and medical activities; (5) to maintain a library of data and reports pertaining to medical research and investigations; (6) to provide our aid and financial aid to recognized schools or institutions of medical education; and (7) to do any and all things necessary or desirable for the attainment of these purposes.

Besides donations to medical schools, there will be an established guaranteed program for medical students, interns, and residents. Financing has been negotiated by the AMA with Continental Illinois National Bank and Trust Company, Chicago. For every dollar set aside by the Foundation as a guarantee, the private banking industry will loan \$12.50; thus, for every contribution we make, there is made available 12½ times the contribution for direct loan. The loans will be repaid, in installments, after completion of medical school, internship and residency.

During 1962 4 direct-mail fund appeals will be mailed from the AMA headquarters. Two of these already have been received. Two more will be mailed this fall.

Your generous support of this program in the past has been proof that Medicine can take care of itself unencumbered by the strings of government.

W. E. G. LANCASTER, M.D., Chairman

Committee on School Health

The Committee on School Health met in Fargo December 9, 1961. Three members were present: Drs. N. S. Williams, R. W. McLean, chairman, and M. H. Poindexter, and Margaret Frenning, secretary. It was discussed whether the work of this committee should be continued or if it should become a part of other committees. A good program of school health will entail an enormous amount of work by both interested physicians and lay people, and it must be supported to succeed. The chairman reported on the Eighth Conference on National School Health held in Chicago in 1961.

The two problems of greatest concern at the present time, according to the National Conference, are: (1) recognizing the emotionally disturbed child in the early stages (it is estimated that 1 out of 10 children has an emotional problem); (2) teachers must be screened and trained so they are able to handle children in the class rooms. In many instances the teachers themselves are emotionally disturbed and, as such, are not capable of handling the children. Teachers' colleges should include in their programs a training course to assist the teacher to recognize emotional problems as they appear. An early separation of disturbed children into small classes and away from the other children is also a matter of importance.

It was felt by the members at this meeting that more information was necessary concerning facilities available in the state and the cooperation of the various departments, including the Department of Public Instruction, before further activities could be carried out.

The chairman met with the Mental Health Committee in Jamestown March 17, 1962, and concurred with its proposed activities in this particular field.

With the apparent lack of interest in the other problems of school health, outside of those being handled by the Mental Health Committee, the lack of facilities in the state, the legislative appropriations regarding both our children's mental health and school health, it appears that this committee must remain behind the scenes until further achievements are accomplished in the educational systems in our state.

A school health meeting is being held June 1, 1962, in Bismarck, and if any questions arise, the chairman will be available to answer them.

R. W. McLEAN, M.D., Chairman

Medical Advisory Committee to the Public Welfare Board

The fall meeting of the Medical Advisory Committee to the Public Welfare Board was held in Bismarck September 30, 1961. Those present were Drs. M. E. Nugent, G. Christianson, G. L. Comtryman, Joseph Craven, R. M. Fawcett, Richard F. Raasch, Frank D. Naegeli, E. H. Boerth, and Mr. Ralph Atkins and Mr. Richard Myatt of the Public Welfare Board.

The committee discussed some specific billing procedures and recommended that when a thoracentesis is performed on a house call, both the fee for the house call and the thoracentesis should be allowed. The practice of routine payment of services for special nursing care in nursing homes was discussed. It was felt that this should be held to a minimum, and that a new nursing home rate, established on a cost basis, should be implemented. Implementation of the new MAA program was discussed, but no negotiation for separate fee sched-

ule was held, as we considered this to be a function of the Medical Economics Committee.

A rather lengthy discussion was held concerning the use of expensive drugs or of drugs whose value has not been established, for the treatment of specific conditions for welfare recipients. It was concluded that no limitation should be established on drugs provided to welfare patients, but that the problem should be subject to review at a future date. The problem of furnishing gamma globulin for inoculation against infectious hepatitis was brought up. It was decided that if such gamma globulin is available from the American Red Cross and the State Health Department, it should be utilized for welfare recipients rather than purchasing this material through security assistance funds. The possibility of a general vaccination for influenza for aged recipients of public assistance was brought out, since this program was urged in a letter received from the Director of Health, Education and Welfare. It was a recommendation of the committee that a regular program of inoculation was not in order, but that individual cases be treated as they occur, and any steps toward inoculation on a large scale would depend upon the immediate circumstances in any given area of the state.

The Welfare Board was advised that the various medical districts in the state had organized a District Medical Review Committee which would be available to consider grievances arising between the various welfare boards and the physicians in that area. Because the council in its December meeting took action terminating the current agreement with the Public Welfare Board, no further meetings of this committee were scheduled.

M. E. NUGENT, M.D., Chairman

Liaison Officer to the North Dakota State Bar Association

Contact was made with the North Dakota State Bar Association in an effort to develop another program similar to those of the past, constituting a medical-legal institute. However, it was determined that it did not appear feasible to do this during the year and attempts were discontinued.

It is hoped that further efforts will be made for the continuation and expansion of these medical-legal institutes.

PAUL JOHNSON, M.D., Representative

Committee on Pharmacy

A meeting of the Committee on Pharmacy was held on December 9, 1961, at the Gardner Hotel, Fargo. Present were Drs. O. A. Sedlak and E. L. Grinnell, and Jim Moore, Vern Wagner, E. M. Sinner, Al Doerr and Daniel Buchanan.

Necessary steps to be taken in establishing a joint public relations effort between Medicine and Pharmacy was the first item of business. Mr. Al Doerr, Mr. Moore, and Mr. Sinner told the group what was being done in Bismarek and Fargo, respectively, and the manner in which individual practicing pharmacists paid for the cost of television broadcasting. Dr. Grinnell said he was in favor of a statewide television broadcast of some kind, and the entire group agreed that perhaps in the future a statewide Medicine-Pharmacy-sponsored program could be undertaken. A resolution was passed that the council be informed that it was the wish of the Committee on Pharmacy that a sub-committee be appointed from mem-

bers of the medical and pharmaceutical associations' committees on public relations to work jointly on public relations.

The committee considered the problem of generic name prescribing. Dr. Sedlak explained the meaning of that type of prescribing, and several of the implications of the proposed Kefauver bill now before Congress. Mr. Wagner asked what the official policy of the North Dakota State Medical Association was in regard to generic prescribing. He was assured that physicians are free to prescribe as they deem fit. Dr. Grinnell added that physicians in the Third District Medical Society prefer to prescribe by trade names. By way of summation, the committee agreed that generic name-prescribing in North Dakota is not a widespread problem, with the exception of a few hospital formularies. Representatives of the pharmaceutical association were assured that physicians would stand behind them should any attempts be made to force generic prescribing.

The fact that mail order prescriptions are becoming a troublesome area was recognized by members of the committee, and individuals were told of problems encountered in their localities with mail order-filled Rx's.

The question of the legality of such prescription-filling was discussed. Committee members learned that a complaint had been registered with the State Board of Pharmacy on mail order prescriptions by pharmacists in the Grand Forks area.

Committee members individually and collectively concurred that they were opposed to the establishment and patronage of mail order prescription houses for ethical, as well as sanitary reasons.

Mr. Jim Moore of Bismarek reported on the progress of "Regulation 19." Regulation 19 is a proposed regulation to be presented to the State Board of Pharmacy to prohibit the dispensing of drugs in hospitals without a registered pharmacist in charge. He said that the Board of Pharmacy could adopt the regulation without its going to the Legislature, and that it would be implemented through the cooperation of hospital administrators and pharmacists in the several local areas.

The committee reaffirmed its earlier opposition to the administration's King-Anderson bill.

O. A. SEDLAK, M.D., Chairman

Liaison Committee to the North Dakota State Dental Association

There has been no activity during the past year. Relationship has remained on an excellent basis.

DAVID JAEHNING, M.D., Representative

Report of Representative to Medical Center Advisory Council

Your representative has attended the 2 regular meetings the past year.

Medical students. Applications are being received faster than in the recent past. To date we have at least 35 more from North Dakota than last year and with apparently better qualifications. It is planned to accept about 47 freshmen this fall. This is 7 more than we have been admitting. It is expected that 43 from North Dakota and 4 from out of state will be admitted in the fall of 1962. There has been no transfer problem for a number of years.

Medical student loan program. Close to \$300,000 is now involved in loans to medical and dental students.

The first repayments have now been made on these loans.

We think that too much has been made of the fact that 10 students of the Class of 1957 have returned to the state to practice. This has happened with previous classes, notably in 1952 and 1950, and a higher percentage than this was attained by some of the earlier classes with a smaller number of students. Accordingly, the Medical Student Loan Fund cannot be given credit for these students' return. More experience will be necessary to establish its effectiveness. So far, 3 students who have received loans have avoided their obligation to return by repaying their loans in full. Accordingly, the status of these loans and the money involved will not be known for a number of years.

It will be interesting to note what impact the American Medical Association Loan Program for Medical Students will have on our loan program. As we understand it, the AMA program will have no strings attached, will carry about the same interest rate, but will have no forgiveness features like those in the North Dakota plan.

Psychiatric training grant program. This is another program which the Medical Center was instructed to offer by the State Legislature. This is not a loan program but a grant for psychiatric training, and it definitely obligates the recipients to return to the state for a few years. Two more physicians who have taken advantage of this program will finish their training in July, 1963, and are obligated to return. As of this writing, no applications for grants under this program are pending.

Faculty. Since my last report, faculty salaries have been adjusted upward, a substantial increase being given all along the line and now they compare favorably with those in other schools. Information available indicates that many other schools are in a position to offer not only larger salaries but various fringe benefits which we do not offer. There are shortages in the departments of anatomy, physiology, bacteriology, and pathology. The latter we expect will be filled soon.

Research facilities. To attract and hold competent faculty personnel it is essential to offer adequate compensation, teaching facilities, and research facilities. The Ireland Research Laboratory has supplied research facilities which rapidly have become inadequate. There is under construction a large addition to this laboratory, which will be completed almost entirely with a grant of \$402,000 from the federal government. Only about \$17,000 of mill levy money will be necessary. When completed there will be a little less than \$70,000 of mill levy funds in this whole laboratory, the rest having been supplied from federal funds, Hill-Burton funds, and the original contributions of Mrs. Guy L. Ireland of Grand Forks.

The Hill research professorship has been filled by Dr. Robert Nordlie, who has been here since December 1961. In addition to the \$75,000 five year grant from the Hill Foundation, there is a \$5,000 grant from Smith, Kline, and French for Dr. Nordlie's use in developing his research program.

Graduate school. This program continues to increase. There are now a total of 31 graduate students. There are 10 in anatomy, 3 in bacteriology, 10 in biochemistry, 8 in physiology, and one fellow in pathology. Sixteen are receiving support from various federal programs, such as the National Institute of Health.

Blood bank. This program continues under scrutiny, with the possibility that it may be discontinued. If so, the Rh testing program will be continued.

Biochemistry laboratory services. This continues to be

a very busy service. The aim is to do only those unusual biochemical procedures which are not generally available through private laboratories.

Medical technology school. This program continues to turn out a small number of well trained medical technicians. There has been no significant change in it since last year's report.

Nursing school. This school is still working toward accreditation and is a very slow-growing department. A teaching grant for teaching psychiatric nursing has been obtained for a four-year period, and efforts continue toward full accreditation. Progress appears to be slow.

Rehabilitation unit. The volume of work continues about the same as the past few years. Reports to me from physicians in close touch with this program indicate the quality of work being done is good but that considerable more could be handled.

About 61 per cent of the patients are referred by physicians, 26 per cent by Vocational Rehabilitation, 4 per cent by Workmen's Compensation, Welfare, and Insurance companies. Out-of-state patients are not taken until arrangements for payment are made.

A change in medical direction would be advisable if a psychiatrist can be obtained, and efforts continue in this direction. At present 3 orthopedic surgeons in Grand Forks spend time each week at the unit, so it is under good medical direction. Consultation with other specialists is available.

The addition for housing disabled patients is about 60 per cent complete as of February 1, 1962. It is anticipated that the work load will increase considerably and be improved with housing facilities for many of these patients in the building itself, rather than in dormitories, rooming houses or local hospitals. If this program follows the pattern of those in other places, we can anticipate it to be 80 to 85 per cent self-sustaining.

Periodically there is consideration of or attempts made to abolish the Medical Center mill levy by either a vote of the people or action of the legislature making the operation of the school subject to biennial legislative appropriation. Such attempts might be made during the next years. The school has been operated in this manner previously, and for those not familiar with its history, and for those who have forgotten it, the following may be of interest.

Due solely to inadequate legislative appropriation for physical plant, faculty, and operation of the medical school, it deteriorated.

In 1931 it was dropped from membership in the American Association of Medical Colleges. In 1939 it was put on probation by the accrediting body for medical schools and was not reinstated until 1951. Its previous good reputation and the leniency of the accrediting board (probably due to Dr. Harley French's influence) kept it from losing accreditation as a two-year school.

In 1949 Medical Center mill levy funds became available. Since that time through what I consider wise use of those funds, the school has been built up both physically and scholastically to the point that we have had since 1951 an excellent two-year school with full accreditation. We have no problems transferring students to other four-years schools, and they make excellent records both in these schools and in the practice of medicine. The school is now in excellent condition and has a good reputation. A recent inspection by the accrediting body resulted in full approval and only minor suggestions regarding the teaching program.

There always has been a shortage of qualified teachers in the basic sciences. At present the competition for such

men in medical schools throughout the country is intense. If we are to maintain present high standards in our school, we have no choice but to meet, and possibly exceed, compensation offered in other schools, maintain adequate teaching facilities, and develop adequate research facilities. In attracting a competent faculty to this school it has been a strong point that the mill levy funds assure the school an income free of the hazards of biennial legislative appropriation.

In my opinion, the solution of Medical Center problems and long range planning can be carried out best by allowing university and school officials, in cooperation with the Medical Center advisory council and the State Board of Higher Education, to use Medical Center funds as they think best without having to rely upon legislative appropriation every two years.

There has been criticism that some individuals feel they don't know what is going on at the Medical School and what use is being made of the funds. The Medical Center is under full control of the State Board of Higher Education. A member of the state board sits on the Medical Center advisory council, and no major changes or construction can be undertaken without approval of the state board. A detailed annual report goes from the school to the state board, and it is filed along with other state board reports in the State Capitol, so it is available to anyone qualified to have the information.

We now have an excellent two-year school with problems similar to those of other medical schools in the country, turning out between 35 and 40 students each year who make excellent records after they leave. It appears to me that it would be most unwise to change the present method of financing, particularly for one which got the school into most serious difficulty not many years ago and which might do so again.

P. H. WOUTAT, M.D., Representative

Liaison Committee to the State Board of Administration

The committee met on two occasions during the past year. At the request of Mr. Joos, chairman of the State Board, a meeting was held on September 7, 1961, at the State Hospital in Jamestown. Attending were Mr. Joos and Mr. Fine of the State Board, and Mr. Henry Lahang and Dr. Schmidhofer of the State Hospital. All members of the advisory committee were present.

One question under discussion was fees for services as well as amount of services to be provided by the pathologist at the State Hospital. It is the feeling of this committee that the state was exceedingly fortunate to have the services of a pathologist, as well as being fortunate, from a financial standpoint, of having the services at such a low salary. The committee recommended that his salary remain the same as it has been in the past, and that the State Board of Administration be ready to increase such salary when he passes his American Board of Pathology examination. Unless this is done, he undoubtedly will move to another institution.

Our committee recommended that any consulting physician working for the state on an individual case basis be reimbursed at the welfare fees scheduled rate.

It was recommended that in the future any physician employed by the State Board of Administration at any institution under its supervision first have a letter of acceptance by the State Board of Medical Examiners. The Board of Administration will notify the secretary of the State Board of Medical Examiners that it is considering such a man, and at the same time request the

applicant to contact the secretary of the State Board of Examiners.

The advisory committee felt that some of the chest surgery now being done out of the state on tuberculous patients could be handled in some of the medical centers here. Mr. Joos stated that the Board of Administration would be glad to cooperate to send cases to these centers where they are capable of doing such work, provided the patient so agreed. It is the recommendation of the committee that any chest specialist interested in doing such work so inform the State Board of Administration and work through it regarding mechanics.

At the request of Mr. Joos, and of Dr. Cuadrado at the sanitarium, a meeting was held in Rugby March 24. The reason for this meeting was to set up some standards for selecting surgeons in the state qualified to do the chest surgery for the state sanitarium, fees, amount of hospital bills to be allowed, and how patients should be allocated to the various surgeons.

There were only 2 members present, at this meeting, presided over by Dr. Carroll Lund of Williston. Mr. Joos, Mr. Levin, and Mr. Fine were there, as well as Dr. Cuadrado.

In the past years, Dr. Kinsella of Minneapolis has been performing all chest surgery at a flat rate of \$200 a case, regardless of the type of surgery necessary. The hospital has been paid from \$20 to \$23 per day for food and hospitalization and any additional expenses if medication was required. Operating room expenses were \$75 to \$125 per case. Anesthetic costs ran about \$20 per case. Some anti-tuberculosis drugs were provided by Dr. Cuadrado. The average hospital stay was about nine to ten days, and the entire cost per case averaged from \$700 to \$750.

The following resolutions were passed.

1. Qualified chest surgeons in North Dakota, not necessarily Board certified, who have proper hospital facilities, anesthesiology, and consultations, will be allowed to perform chest surgery. Notify all qualified chest surgeons in the state to send their qualifications, training, history, and records to Dr. John C. Fawcett, chairman of the advisory committee, Devils Lake. These will be reviewed by the Medical Advisory Committee.

2. The advisory committee refer the subject of surgical fees to the Committee on Medical Economics of the state association for its decision as to an acceptable fee, keeping in mind the previous fee of \$200 to Dr. Kinsella; also keeping in mind the obligation of the medical association to aid and contribute to the eradication of tuberculosis in North Dakota.

3. The amount of hospital fees to be arrived at by an agreement between the chest surgeon, the individual hospital, and the State Board of Administration. (The committee felt that it was impossible to arrive at a definite fee, as these fees will vary in different hospitals.)

4. Dr. Cuadrado to be considered the No. 1 consultant in preoperative and postoperative cases, and an integral part of the surgical team.

5. Dr. R. H. Kinsella of Minneapolis to be retained as a senior consultant, and that the advisory committee and the Board of Administration send him a letter of gratitude for the tremendous amount of help he has contributed to North Dakota in the program of tuberculosis control.

6. Each patient to have a personal choice of chest surgeon. In the event that the patient does not have any choice, a surgeon will be chosen in whose geographical area the patient resides.

It is the feeling of this committee that there has been

very good cooperation between the State Board of Administration and the heads of the various state hospitals with your committee. I see no reason why this should not continue.

JOHN C. FAWCETT, M.D., Chairman

Committee on Cardiovascular Diseases

The committee met at the Gardner Hotel on December 9, 1961, with the chairman, Dr. Robert M. Fawcett, presiding. The following were present: Drs. R. M. Fawcett, R. D. Story, Mack V. Traynor, Roy Amos, C. A. Hamilton, and Mr. Warren L. Dumtley and Mr. Tom Burgum.

Dr. Fawcett opened the meeting by defining the purpose of the committee as a liaison group between the North Dakota Heart Association and the North Dakota State Medical Association.

He reported that in accordance with a recommendation of this committee at the 1960 meeting, the North Dakota Heart Association held a scientific session for physicians of North Dakota in Minot November 14, 1961. The topics and speakers were excellent, and were of importance to those in attendance. Thirty-one physicians attended. The committee was in complete accord in urging all North Dakota physicians to attend the annual scientific session of the North Dakota Heart Association as one means of keeping abreast of current concepts in cardiovascular diseases.

Dr. James V. Miles proposed that the committee consider a symposium dealing with the recognition of congenital heart defects in children, to be presented under the sponsorship of the North Dakota Heart Association, to the physicians of North Dakota through the 10 medical district meetings. Dr. Hamilton suggested that the program would be of particular value to the general practitioner, in that accurate recognition of basic symptoms would lead to referral for further evaluation. Dr. Story indicated there is a definite need for this type of professional education, and that the medical district level meetings would insure best coverage of North Dakota physicians. The committee indicated approval of this proposal, if implemented by the Heart Association.

Dr. Roy Amos, State Health Officer, reported on the activities of the Rheumatic Fever Prophylaxis Program after two months of operation. As of December 7, 1961, 187 patients had been registered and placed on the low-cost medication. Of the total number of patients, 30 per cent were on injectable bicillin, 68 per cent on oral penicillin, and 2 per cent on sulfadiazine. Few, if any, problems in the mechanics of the program were noted. Dr. Amos concluded that "it might be assumed that more individuals have been placed on continuing medication as a result of the low-cost medication." In answer to specific questions regarding the role of the public health nurse in follow-up visits on patients enrolled in the program, Dr. Amos emphasized that they would act only on the recommendation of the family doctor.

Warren L. Dumtley reported on plans for a pilot project in physical therapy for the stroke patient which will be conducted in Williston shortly after the first of the new year. The plan includes training the nurses of the area in the basic principles of physical therapy so it may be carried into the hospitals and homes dealing with stroke patients. This program also is being implemented upon the recommendation of this committee at its 1960 meeting.

Dr. Amos reported on the project of the North Dakota State Department of Health in which the heart sounds

of 3,400 children of the Dickinson public school system have been tape-recorded for evaluation of heart damage. The project is a result of the 1961 outbreak of rheumatic fever in the area and is being conducted with the aid of equipment loaned by the U. S. Public Health Service. After recording, the tapes are sent to Chicago for evaluation by two physicians who have been involved in similar programs in Chicago schools. It was the consensus of the committee that inadequate information was available at present for the committee to take a stand of approval or disapproval of such a project. Dr. Hamilton made the point that such a study is still in the field of experimental research.

R. M. FAWCETT, M.D., Chairman

Liaison Committee to Blue Cross-Blue Shield

This committee had no formal meetings the past year. There was, however, a certain amount of activity aimed at the exchange of ideas in order that there might be a better understanding between the members of the medical societies and Blue Cross-Blue Shield.

It seems that each year the news media, the government, and the general public place more and more emphasis upon the cost of medical care. When people mention medical care costs, they are referring to hospital costs and drug costs, as well as the cost of doctor care. Thus, directly or indirectly, we are concerned about all of these costs whether we like it or not.

We know that most doctors are honest and that few are interested solely in money. We know that all in the health fields live by ethical standards that are the highest for any profession. But does the public know this? We know that most doctors and hospital administrators are devoted people trying to do the best job for their community. But, here again, is the public certain of this? Frankly, the public—which we all serve—has raised a number of questions about doctors and hospitals and about Blue Cross and Blue Shield. Some are provocative questions, with overtones of disrespect for the health profession, which is unique in our time. The questions have been raised seriously and they come from the whole public—editorial writers, labor leaders, management people, farmers and others. If the public believes there is abuse of Blue Cross and Blue Shield and asks questions about this, we must provide the answers. If we do not provide the answers to their satisfaction, we must not be surprised to see the government move in. If there is waste, abuse, overuse, or overcharging, these conditions should be identified and proper steps taken to see that they do not recur.

A year ago the report of this committee included a recommendation that each district society form a review committee that would work with Blue Cross, Blue Shield, commercial insurance companies, and the public to review any problems that might arise in relation to claims or payments, and to answer any questions the people might have. Most of the district societies now have these committees, but as yet they have not become operational. The societies that have not appointed such a committee should do so posthaste. However, the fact that these committees are formed will not solve any problems. We must let the public know we have these committees. We must let the people know that Medicine is ready, willing and able to handle problems relating to health care and to health care costs. The State Medical Association has the facilities to tell the public that these committees are formed and ready to go to work. We feel that the direction and operation of these committees must come from

the state society. The activation of these committees and the attendant publicity could be the greatest step we can make in letting the people know that the medical profession is doing everything possible to insure the people that they are getting the maximum benefit from their health care dollar.

O. A. SEDLAK, M.D., Chairman

Committee on Emergency Medical Service

A meeting was held on December 8, 1961, at the Gardner Hotel, Fargo. Rather than read the minutes of the previous meeting, the deliberations of the committee were discussed by the chairman, with emphasis on the fact that this was the first meeting of this group and that it was without direction. Also, because this is a relatively new committee and a complete change of members present at this meeting, the purpose and hoped-for function of the committee were discussed briefly.

The chairman presented the proposed activity for the coming year with the following:

1. Sponsorship and the establishment by the medical profession of an emergency medical program to be offered throughout the state. This will be accomplished by the use of the Civilian Defense effort by the Department of Health, Education, and Welfare at a national level. A self-help emergency medical teaching kit will be made available by January 1, 1962, which will be used by doctors of the state to formulate the program. It will be the responsibility of this committee to establish the teaching mission by using representatives from each local medical society. It was pointed out by the chairman, that it is the intent of the Civilian Defense effort that medical societies, as well as the individual practicing physician, provide the professional leadership and guidance necessary to support this training program to insure the highest quality of instruction obtainable.

This program has been approved by the A.M.A., and all state societies are urged to participate as per communication from Dr. Blasingame.

The training kit has been designed and developed to contain everything needed for teaching the lay public the rudiments of survival principles.

The medical profession has an opportunity to make a significant contribution to strengthening our Civil Defense capabilities by supporting this program and offering all possible cooperation in its conduct. It is believed that every physician has a solemn duty and obligation to assist in preparing the public for civil defense readiness. It is also the contention of your committee that excellent public relations will be achieved because of the timeliness of the program and its being kept under the auspices and guidance of the medical statute.

2. The formulation of a hospital emergency plan which would be made available to all the hospitals of the state. They could incorporate it into their existing plans or base their plan around the one presented.

The program was accepted on motion of Dr. Lindsay and seconded by Dr. Nuessle, and the chairman was directed to present it to the council on December 9, 1961.

The council accepted the committee's recommendations and gave an immediate approval for the implementation of the program.

It is the wish of this committee to thank Mr. Lyle Limond and Daniel Buchanan for their most considerate and efficient help and advice in the implementation of its recommendations.

RALPH E. MAHOWALD, M.D., Chairman

Report of the Delegate to the American Medical Association

I was in attendance at all sessions of the House of Delegates last year and various meetings of the Council on Medical Service and related committees.

Dr. Leonard Larson of Bismarck assumed the presidency of the association in June 1961. He has continued to work tirelessly and effectively for the A.M.A. Dr. Larson spoke at the clinical session in Denver, clearly and effectively denouncing the political proposals of the present administration. We have every reason in North Dakota to be proud of Leonard's long years of service to the association and his leadership during his term as president.

There has not been, and there probably never will be, any letup in the strenuous campaign being waged by organized groups and individuals which have for their ultimate purpose complete control and direction of everything concerned with the provision of medical and related services in this country. Members of this group in general seem to feel that the assumption of over-all control by the federal government as paymaster and director would be desirable. We must face the fact that powerful political forces led by the new ruling family dynasty are working energetically with Irish enthusiasm toward this end. Currently, the effort is directed toward the votes of 17 million older citizens, but no doubt eventually they will be reaching out for the family vote.

It is to me regrettable that much dynamic leadership for this point of view is being provided by a relatively small group of physicians and an increasingly large number of persons engaged in closely related health fields. Most of these physicians are working in the area of medical administration, teaching or public health. Those in practice are in many instances connected with closed panel prepayment plans.

The Medical Care section of the American Public Health Association is dominated by these individuals. This provides them a forum for discussion. In addition, their arguments are presented in public health, welfare, hospital, labor, and some nonmedical publications. In general, this group presents the following ideas:

1. More federal spending for medical care plus definite federal controls.

2. Complete medical care under a comprehensive prepayment insurance program, with its main feature being closed panel provision of services.

3. Medical care in general should be provided by doctors working for a salary rather than fee for service.

4. The hospital should dominate increasingly all medical care in the community, and in general, doctors should be full time employees of a hospital.

5. A solo practitioner cannot and does not provide a good quality of medical care.

6. Hospital boards of trustees and other lay groups are qualified to judge the quality of medical care.

7. Voluntary prepayment insurance as presently constituted is inadequate.

It hardly needs to be said that all these persons are in favor of the Kennedy social security approach as an initial step toward a more complete federal program.

I would commend to your attention articles by Dr. M. Cherkasky, medical director of Montefiore Hospital in New York; Dr. Milton I. Roemer, director of hospital administration, I believe, in one of the California medical schools, and Dr. C. Esselstyn, director of the Rip

Van Winkle clinics in New York State. These articles appear usually in public health or hospital journals.

It is difficult to estimate the number of practicing physicians who follow this type of thinking, and I would doubt that their point of view would have any appeal for the vast majority of doctors in North Dakota.

One of the great difficulties presented to organized medicine at the present time is the extreme fragmentation of the profession. There are a large number of specialty groups, all of which, to some degree, try to represent the special interest of their particular group. This would apply to surgeons, general practitioners, internists, pathologists, radiologists, and other groups. I am sure this is quite understandable, but sometimes it seems that the over-all activities of each and every special group within the profession tend to weaken the AMA as an organization representing the entire medical profession. As an example of this situation, the recent controversy between the American College of Surgeons and the American Medical Association and other interested groups points up this situation. At the clinical session of the House of Delegates, held in Denver, the House agreed with the intent of 5 resolutions which expressed strong dissatisfaction with a recent statement by a spokesman of the American College of Surgeons, Dr. Myers. The spokesman stated in effect that much poor surgery was being done by unqualified persons, that is to say, persons who are not members of the college. He also criticized the ethical position of the AMA regarding payment of surgical fees under insurance programs. A great deal of indignation was expressed by various members of the association, and the reference committee in its report stated:

"Your reference committee believes the public airing of disagreement between large segments of medicine can only confuse and shake the confidence of the public in the medical profession and distort the true image of Medicine which the American people should have. Meetings between the board of trustees of the American Medical Association are being held, and it is hoped that agreement may be reached, at least on the matter of public statements of policy."

The House of Delegates is on record that effective discipline by the profession of a few members is necessary. There is still disagreement as to the best method to adopt in carrying out this objective. The Medical Disciplinary Committee of the board and the Council on Constitution and Bylaws presented a proposal which would have changed the bylaws so as to confer original jurisdiction on the association to suspend or revoke the AMA membership of a physician found guilty of violating the ethical policies of the association, whether or not action had been taken against him at the local level. This proposal was laid over for further consideration.

A proposal from one of the state associations that state and federal funds be provided for voluntary prepayment health insurance protection for the aged was referred to the Council on Medical Service for further study.

At all recent meetings of the association, dissatisfaction with the operations of the Joint Commission on the Accreditation of Hospitals has been expressed. The great difficulty seems to be in the interpretation of commission regulations by hospital administrators, doctors and the commission's own inspectors. Criticism comes primarily from those who are connected with nonteaching hospitals and the smaller hospitals where perhaps it is more difficult to carry out all of the commission's recommendations. The speaker of the House is to appoint a com-

mittee to restudy the entire program of accreditation of hospitals.

Dr. George M. Fister of Ogden, Utah, was elected president-elect, and will succeed to the office of president in June 1962.

In concluding this report, I again draw attention to the fact that those of us who believe in the freedom of the individual and the private practice of medicine as the best way of life are continually being faced with many perplexing unsolved problems. If our way of providing medical care is to be preserved, continuing and unceasing effort must be extended by those, and I think this includes the vast majority of our profession, who sincerely believe that it is the better way. It has been a great privilege to serve as delegate to the American Medical Association for these many years, and I would like to draw your attention to the fact that my alternate delegate, Dr. Thomas E. Pederson, has been attending many of the meetings and is becoming more and more familiar with the work of the association.

WILLARD A. WRIGHT, M.D., Delegate

Report of Representative to the Crippled Children's Services Division of the Public Welfare Board

This committee met November 4, 1961 in Bismarck. Members present were Drs. B. J. Clayburgh, A. R. Gilsdorf, D. T. Lindsay, James V. Miles, C. H. Peters, Alice H. Peterson and Donald E. Skjci. The Public Welfare staff present were Dr. Paul L. Johnson, Dr. T. L. Stangebye, Mr. Carlyle Onsrud, Mr. T. N. Tangedahl, and Miss Margaret Lister.

The categories of this meeting were as follows:

1. The cardiac phase of the program was discussed first, centering around (1) general management of cardiac cases in reference to local and regional centers, and (2) the extent of providing support of care for children with cardiac problems.

The general management of cardiac cases was brought up because of the one area in the state which has been set up for heart catheterizations and the possibility of the second area developing the same program. Dr. Peters felt that there should be consistency in the policy of out-of-state referrals in respect to cardiac patients as well as problems in other specialties. Dr. Clayburgh indicated that he felt that encouragement should be given to the use of cardiac facilities within the state, but it should not be a requirement.

In respect to the extent of providing support of care for children with cardiac problems, Dr. Miles stated that he thought there was a void in informing parents as to the extent of Crippled Children's Service responsibility for children with cardiac problems. He suggested the possibility of approaching the need for supported care as it is done in the case of catastrophic insurance plans, that is, the family or general assistance pays up to a certain amount and then Crippled Children's Service assumes financial responsibility. Dr. Peterson raised the question whether the Crippled Children's Service is in a financial position to undertake the care. Mr. Tangedahl stated that the budget does not allow for support of care at the present time, but if it were to be included in the Crippled Children's responsibility, we should plan now for the budget to be drawn in two years.

2. The second general category was discussion of the increasingly costly per diem hospital rates. Dr. Johnson cited the 15 per cent increase in physicians' fees in the

last eight years and indicated that he did not feel we should subsidize increasing hospital rates to the extent that is presently being done by authorizing the rate calculated in accordance with the reimbursable cost formula of the Children's Bureau. Attention was given to a chart which showed 100 per cent increase in most instances and up to 200 per cent increase in rates for some hospitals. He mentioned that the South Dakota Crippled Children's program uses the hospital per diem rates calculated from this formula in terms of payment for a designated number of days in surgical cases, and pays a reduced amount of \$15. per day thereafter. Dr. Lindsay suggested that the Crippled Children's Service pay a designated amount per day, for instance \$15 per day, the balance of the hospital charge being the responsibility of the family or general assistance if the family is unable to meet the cost. Dr. Peters raised the question of differences in hospital costs within the state, and it was explained that they principally were due to (1) hospital building programs and (2) decreased utilization of hospital facilities. Dr. Lindsay raised the question why the State had not built a hospital in view of the state expenditure for hospital care. There was unanimous concurrence that this group's concern should be brought to the attention of the hospitals, along with terms of their increasing rates and the need for consistency as to how items are classified in charging and auditing hospital records.

3. The third general category was discussion of out-of-state referrals. The group felt that the present policy, providing that treatment by out-of-state physicians can be authorized only when requested by a physician authorized by the Crippled Children's Service in the specialty involved, is satisfactory. There was no recommendation for any changes in this policy.

4. The fourth category was a discussion of mean tests for Crippled Children's Service. Mr. Tangedahl said that discussions with the field staff of the Public Welfare Board had resulted in the suggestion that the board, rather than just the director, pass on financial eligibility. He believes this procedure would correct the present abuses, but there are also some disadvantages. Dr. Miles felt that a means test was psychologically wrong, and he mentioned the possibility that the county be financially responsible in the matter, similar to a deductible insurance plan, and that Crippled Children's Service be considered after the parents and county have paid a certain amount of the medical expense. Dr. Stangebye pointed out that it would be helpful if the physician would indicate the approximate cost, since it is not possible for any one physician to be well informed of treatment costs in all specialties. He said that if the treating specialist questions the decision made by the medical director of the Crippled Children's Service, the Service may be able to explain to the physician some factors which had gone into the decision which might not be known to him. The consensus of the council was that the recommendation on the Crippled Children's Service application should be that of the County Welfare Board.

5. A fifth category was cost of supplies by vendors of glasses or braces. The general consensus was that contact lenses were usually a luxury but may be justified in an occasional instance if medically indicated. Dr. Lindsay said that chrome plating on braces might not be a justifiable expenditure by the Service.

6. A sixth category was submission of authorizations for payment. Dr. Johnson mentioned the difficulty Crippled Children's Services had in getting authorizations

returned for payment at the end of the fiscal cutoff periods, and that the Public Welfare Board had requested that this be brought to the attention of the council for any suggestions it might have as to how the situation could be alleviated or improved. Dr. Lindsay suggested the importance of authorizations coming directly to the physician rather than the business office. Mr. Onsrud mentioned that clinic business managers at their statewide meeting in Bismarck in 1961 had suggested the possibility of arranging a meeting of Welfare business office personnel involved in the authorization and payment process. It was his opinion that this suggestion should be carried out. Dr. Clayburgh mentioned that, if deadlines or if specific cuts were to be established, this would be an additional handicap to physicians who already are providing care at reduced costs.

7. The seventh category was consideration of possible changes in the scope of Crippled Children's Services.

Hypogammaglobulinemia. Dr. Miles felt that it would be cheaper in the long run if this condition can be diagnosed properly and children treated on an outpatient basis. He did not believe that the Crippled Children's Service should be involved in the diagnostic service for this condition.

Epilepsy. Dr. Miles stated that he did not believe that the Crippled Children's Service should include epilepsy in the listing of conditions for which treatment can be provided from program funds. It was felt that the Service should cover the cost of a diagnostic work-up and determination of a case of brain tumor. When Crippled Children's Services should authorize diagnostic work-up in this connection should be left to the judgment of the medical director of the program.

Thyroglossal cysts. Dr. Gilsdorf suggested that he did not believe that it was necessary for this condition to be included in the medical scope of Crippled Children's Service program.

Hearing aids. Dr. Lindsay said that it was his impression that in many instances service clubs are providing hearing aids when parents are unable to purchase them from their own funds, and inquired if Crippled Children's funds services had evidence that there was any unmet need in this area. Dr. Miles indicated that, unless we have factual information that there are children needing hearing aids who are not being cared for, this should be explored further before Crippled Children's Service expands the program to include them.

DONALD E. SKJEI, M.D., Representative

Speaker Christoferson presented to the assembled delegates the president of the Woman's Auxiliary to the North Dakota State Medical Association, Mrs. Rosemary Longmire of Devils Lake.

Her report follows:

It is an honor and a privilege to present this report to you on the accomplishments of your auxiliary for the past year.

The auxiliary was asked by the state association and the American Medical Association to participate actively in opposition to the King-Anderson bill. On February 17, the WHAM campaign was launched with a successful workshop in Fargo. The Dr. Annis film, "Where is American Medicine Going?", has been shown on 3 TV channels through the combined efforts of the auxiliaries and societies in the respective districts. It has been shown at several district meetings and at public gatherings. The Ronald Regan record, "Operation Coffeecup," has been used in all the districts. Hundreds of letters

opposing the Social Security approach to medical care financing have been written to our congressmen and senators.

The Sophomore Medical Students' Loan Fund continues to be a top priority project. This year \$2,746.57 has been contributed, bringing the total assets of the fund to \$23,598.32. AMEF contributions have increased 72 per cent over last year, with \$1,130 being sent from the auxiliary. The auxiliary to the North Dakota Student Medical Association received \$100 from us this year to help defray expenses of the delegate to its national convention. One of their members, Mrs. George Ward, won recognition at the convention by having her design entry named winner in a national contest. It will become the official emblem for the Woman's Auxiliary to the Student American Medical Association.

Our membership totals 331, almost 80 per cent of potential. Every auxiliary member in North Dakota is an ambassador of good will for the medical profession through her efforts in community service. In our rural state, every locality knows its doctors' wives. Their efforts do not go unnoticed, and they reflect favorably on the auxiliary and on Medicine.

News, Views, and Cues is published 4 times a year. It is sent to all members. Reports from committee chairmen, news from the AMA, messages from the presidents of the association and the auxiliary, and material from AMPAC were included in the issues this year. Advertising to cover the cost of mailing was procured this year for the first time. North Dakota Blue Shield is our advertiser.

Recruitment for health careers received special emphasis this year. Each auxiliary member contacted the high school guidance counselor in her city, offering her services to students interested in medicine and related fields. We cooperated with the North Dakota Council on Health Careers in placing kits of information in the hands of high school counselors. A Health Careers Rally was held in Bismarck in September, sponsored by the North Dakota Council on Health Careers. Auxiliary members assisted in the preparations, and clubs from 4 districts were represented.

We look to you for guidance and assistance. We appreciate the cooperation we have received from you, your president, and from Mr. Limond and his staff. We are proud to be your Auxiliary and to have a part in helping to celebrate your seventy-fifth anniversary.

Speaker Christoferson asked that the association go on record extending sincere gratitude to the Woman's Auxiliary for its efforts of 1961 and 1962.

Dr. L. W. Larson, the president of the American Medical Association, was introduced.

His remarks follow:

I appreciate very much the support I have received from the North Dakota State Medical Association, and I hope that when my term of office is over, in about three and one-half weeks, I can not only get back to work, but also take a more active part in the affairs of organized medicine on the state level than I have been able to do in the past few years. I can assure you that this past year in particular has been an interesting experience.

The fact that we now have Mr. Kennedy and his forces on the run, I think, is testimony to the fact that the program as carried out by the American Medical Association through the good offices of the state medical societies, district and county societies, and last, but not least, through the membership of the American Medical Association, has begun to pay off. We at headquarters

always have been optimistic over the outcome, but it seems to me that the climax came a week ago. The President's appearance and speech in Madison Square Garden was anything but high caliber. The interesting thing there was that no one was able to get a copy of his prepared speech. We, and others, were put off from Saturday morning until 2 p.m. Sunday. Now we are wondering if his speech ever was written, because it was perfectly obvious that he talked off the cuff, as he made some very bad blunders. Wednesday, following his Sunday appearance in Madison Square Garden, he admitted in his press conference that the response to his appeal had not been very encouraging. He said that responses received were running about 50-50. That was quite an admission. However, as a result of our appeal, we received 23,800 letters, telegrams, and postcards, and in a preliminary survey, they ran about 90 per cent favorable to our position and 10 per cent against.

One would expect to get a good response, I suppose, on the part of our membership and friends, although there were some pretty nasty letters and telegrams. However, Congress has had such a flood of telegrams, postcards, and letters during this week over this issue that the Postal Department did not have enough trucks to haul these to the House. It is running overwhelmingly in our favor. The reason is simply this: the doctors have gotten aroused over this issue, and the public has gotten aroused, and they are letting Congress know how they feel. Let us not worry about the image of the physician and the American Medical Association. When you are right, as we are, you get support. Our problem is to get the information to the public, and I know in North Dakota that you are doing so.

I have been on the road since April 23, not having been home since then. The response has been magnificent. We were confronted with reporters wherever we went. However, the press most favorable to us is in Chicago.

We cannot relax for one moment. We have to keep on fighting and bringing this to the attention of the people. I am confident that within thirty days or less, and I hope it comes before the meeting in Chicago, this bill is going to be killed in the House Committee by a vote of 15 to 10. So do not be down-hearted, and keep a stiff upper lip. Let us keep up the good work of informing the public of our position, and I am sure we are going to come out on top. When we win, as we expect to, we have a job to do; that is, to continue to sell good medical care to the public. We must provide the best medical service in the world, at a price the people can afford to pay. I get some terrible letters with complaints in which physicians are accused of overcharging, not making house calls, and not being compassionate. That is in the minority, it is true, but we still have a job to do to see that our "Blues" work. Voluntary health insurance is the answer. We must live up to what we have been preaching during this campaign—that every person should have the best care possible, no matter what he can pay.

I was in New York last night and spoke at the Geriatrics Society meeting. Representative Fogarty was there, and he and I are very friendly. I was amazed to have him get up and pay some nice compliments to me. But one thing he said was, "I cannot understand how anyone who is as nice a fellow as Dr. Larson, can, at the same time, be a Conservative." I replied, "I cannot understand why anyone as nice as Mr. Fogarty can be a Liberal." He feels the public should be pulled into the problems of Medicine more than it has been in the past.

and he wants a commission to study the problems of the aged.

You all heard that we went to see the President. That was an interesting experience. I had been in the presence of only one president before; Mr. Eisenhower. We got in to Washington on April 30, only to find that Mr. Salinger, press representative for the President, had issued a statement to the effect that the President had not invited us to a conference, and that if we wished to see him we would have to request a conference with him. That was something new and did not agree with the understanding we had. It was not at all in accordance with the letters we had received. So, what to do? Should we go home, or make a request to see the president? It became a very lively issue, and the Washington papers were full of it. We decided to go to the White House and present ourselves at the gate to which we had been directed, and if we were not supposed to be there, we would turn around and go home. We went to the northwest gate and there was no question about our having an appointment. We were brought in and Mr. Jones was there to greet us. He immediately started apologizing for what had happened. He was the intermediary between the President and us. He said, "I am terribly sorry for what happened, but we are new in this business and we do not understand how these things are done."

Finally we were brought in to see the President. He was very cordial and very nice. He put us at ease immediately. He sat in that famous rocking chair and we seated ourselves on couches. Then there was a dead silence. Finally I started the conversation. I told him I had written him on 2 occasions, once to ask him to be a speaker in Chicago in October at the Mental Health Conference. I urged him to accept the invitation. President Kennedy said he was interested and would try to make it.

He then started to discuss health care for the aged. He said he did not expect to convince us or to have us convince him. But he belabored the point, and I think he was looking for a compromise. He said that something was going to be passed, because this is a political year and a political issue. Dr. Annis jumped right in and said that this was certainly unfortunate. President Kennedy then made the most fantastic statement in argument for the King-Anderson bill and in opposition to the Kerr-Mills bill—that if the Kerr-Mills bill were implemented in every state, it would bust the federal government. His argument is that every state will try to extend the benefits and there would be no controls. Mr. Ribicoff stated that the government is going to have to pick up the lion's share of this bill, and it is going to get just as bad as two others, and he mentioned both the Farm bill and the Veterans bill.

It amazed me that the administration would be talking about two of the things that are draining the United States Treasury. I have never read anything that has stated he has tried to cut down that cost. I told him that every congress has increased the benefits and increased the taxes. He replied that the public never objected to these. I do think he was looking for a compromise, as he said that when this bill is passed, or something like it, tied in to Social Security, he hoped the medical profession would reconsider its position. That to me was an invitation to talk about this now. However, I said, "You have been misinformed. Mr. President, as the bill is not going to pass."

There were about 50 reporters there when we got out of the building, asking what we said and what the President said. We gave them no information. When we got

to Chicago, the only interest the newspapers had was whether we had been invited, or did we have to request the conference.

It has been a pleasure to serve American Medicine and to contribute a little—and I say very little—because if it were not for the staff, the Board of Trustees, the House of Delegates, and you, who have been working on the local level, we would not get anywhere.

The power of the American Medical Association is through the individual physician and what he can do through his patients and his friends, not only in the way he conducts himself, but the type of professional care he gives.

Dr. E. H. Boerth, retiring president of the State Association, was presented.

His address follows:

Since the North Dakota State Medical Association is celebrating its seventy-fifth birthday, I thought it might be appropriate to look back a bit and review some of the high lights and problems of the association during the past twenty-five years. For this purpose I have delved into the proceedings as recorded in the *Journal-Lancet*.

The many new activities of the association have necessitated an increase in dues. Twenty-five years ago the annual dues were \$5.00. In 1939 there was a \$5.00 increase. That same year the subscription price of *J.A.M.A.* increased to \$8.00. In 1940, at a special session of the House of Delegates held at the time of the annual meeting, it was voted to have a membership canvass in order to increase the state dues to \$20, but the general membership voted against the increase. Dues were increased to \$35 in 1945 in anticipation of having a part-time executive secretary, who assumed his duties in 1946. Dues were increased again to \$50 in 1949, and in 1954 more money was needed to accomplish desired objectives, so dues were increased to \$75. The present annual dues of \$100 were voted in 1960.

The increase in dues was necessitated by an increasing budget. For example, in 1945, when a full-time secretary was being advocated, the budget was \$3,200. In 1952, when a full-time executive secretary was selected, the budget was \$17,300. In 1962 the proposed budget was \$43,225, an increase of 150 per cent in the past ten years.

Formerly there were 3 or 4 sessions of the House of Delegates at the annual meeting. Now there are 2 sessions, except for some emergency. The president of the state association was the presiding officer at the House of Delegates sessions, but in 1940 the constitution provided for a Speaker of the House, to be elected by the members of the House at its second session each year. The Vice-Speaker of the House was provided for in 1949. The 1940 constitution also stipulated that there should be one delegate for each 25 members of the district society. Provision was made for 10 councillor districts. The present councillor districts were specified in the amended constitution in 1949.

The 50 Year Club was inaugurated in 1949. Previously the association had an honorary membership for physicians licensed to practice in the state for fifty years. It was felt that recognition should be given to doctors of medicine who had engaged in practice for fifty years, not necessarily within the borders of the state.

In 1956, the association became incorporated as a nonprofit corporation.

Twenty-five years ago there were 17 committees of the association. Now there are 36: 9 standing committees, 18 special committees, and 9 advisory and liaison committees. Several committees are no longer in existence.

such as those concerned with tuberculosis, polio, venereal disease, fractures, pneumonia control, and industrial health. Liaison committees began being formed in 1956 because it was felt that there should be cooperation between the state association and other organizations.

I would like to have you reflect upon the activity of the Medical Economics Committee in the past as related to this committee's present problems. In 1938 work was directed against efforts to modify the Medical Relief Program and against the action of some county welfare boards to reduce medical fees arbitrarily. It must be remembered that at that time the State Public Welfare Board did not have direct control over the various local county welfare boards. A North Dakota Farmers' Mutual Aid Corporation was in existence, and it allowed funds on the basis of \$1.00 per month per family for physicians' and surgeons' services. When the total bills for a given month were more than the amount allotted, each bill was reduced in the proportionate amount. Some months the physicians received very little for the work they had done. The Medical Economics Committee recommended that the fee schedule be rejected and the House of Delegates approved their recommendation.

The executive secretary of the Public Welfare Board was contacted in 1943 regarding a general revision of all board fee schedules. He welcomed the appointment of a Medical Advisory Board and The Medical Economics Committee recommended such a board of 5 members, to consist of 3 from the Medical Economics Committee, 1 from the Crippled Children's Committee, and 1 from the Committee for the Blind. The following year county welfare boards were advised by the State Welfare Board to adopt the fee schedule suggested by the Medical Economics Committee and the Medical Advisory Board, but the county boards were not obligated to do so. The Medical Economics Committee suggested that each member of the House of Delegates urge his local society to endeavor to have the fee schedules adopted in the various counties.

Extensive negotiations with the Public Welfare Board relative to the fee schedule were conducted in 1948. The report of the Medical Economics Committee for that year contains a statement which is as pertinent today as it was at that time: "The rise in the Social Security system has introduced the concept that individual charity is no longer a duty of either the American people or the American medical profession. To the contrary, the federal government promotes the concept that indigents are recipients of all the services provided by the federal government as a matter of absolute right."

A new fee schedule was adopted by the State Welfare Board in 1950, but it did not become effective because the various county welfare boards did not have the money to increase payments to physicians. In 1954, the Medical Economics Committee reported that a satisfactory fee schedule had been adopted by the State Welfare Board and was in operation, the schedule being uniform for all doctors in the state. Thus ended a period of negotiation which lasted over ten years.

In 1960, after a period of negotiations with the Public Welfare Board, a new fee schedule was adopted. At this time an advisory committee of the state association to the board was set up, consisting of 8 physicians from various parts of the state.

The medical Economics Committee's negotiations with the Workman's Compensation Bureau have been the opposite of those with the Public Welfare Board. In 1959, negotiations were conducted regarding a new fee schedule, and although the bureau did not adopt the schedule

which the North Dakota State Medical Association had approved the previous year, an increase in fees in most categories was granted. In 1961, a general revision of fees was made, and increases were made to the satisfaction of the committee and the Workman's Compensation Bureau.

The Medical Economics Committee has been active in prepayment plans for medical care. In 1940, it discussed a plan for medical care only, at a premium of \$17 per family. The following year, at the request of the committee, the president of the state association appointed a committee to study the question of medical service plans. The members appointed were those who were serving on the Medical Economics Committee, and after a study of medical service plans, they felt that prepaid medical care was not likely to succeed in North Dakota at that time. Three years later the committee reported that feeling was that the time was not ripe for a prepayment plan. Perhaps the committee's evaluation resulted from the skepticism many physicians had regarding Blue Cross, which was then in existence.

The Enabling Act for a prepaid medical insurance program in North Dakota passed the legislature and was signed into law February 28, 1945. The 1945 Proceedings of the State Medical Association contains a lengthy report by the Medical Economics Committee which included bylaws of the North Dakota Physicians Service, along with the schedule of surgical and obstetrical benefits. There was a lengthy discussion in the House of Delegates, and finally the report of the Committee was not adopted, with "at this time" inserted. The Cass County Medical Society put into operation in Cass County the prepayment plan developed by the Medical Economics Committee which became effective February 4, 1946.

In 1947, the Medical Economics Committee recommended that the North Dakota State Medical Association associate with and extend the North Dakota Physicians Service Plan which was then in effect in Cass County. Two years later the Committee reported some expansion of the plan throughout the state, but noted that certain district medical societies had not approved the program. The Committee adopted a so-called Partial Income-Partial Indemnity plan, with enrollment limitations of \$3,000 for single persons and \$5,000 for families. A Subcommittee on Prepayment of Medical Care was formed, and it functioned until 1958, when it was decided that the Medical Economics Committee as a whole could handle prepayment problems. Today the North Dakota Physicians' Service Plan has enrolled approximately 27 per cent of the population of North Dakota.

The Committee on Medical Education has been vitally interested in having a good accredited medical school at the University of North Dakota. In 1938, the Council on Medical Education of the American Medical Association dropped the medical school from its approved list but, under protest, the school was placed on probation. The 1945 session of the legislature established a medical center at the university and provided for the Medical Center Advisory Council. This council recommended establishment of a four-year medical school, but after much serious deliberation, the Committee on Medical Education decided it was not feasible to establish one and so reported in 1950 to the House of Delegates. Weaknesses in the medical school were pointed out, especially in physiology and pharmacology, psychiatry, physical diagnosis, biochemistry, animal experimentation, and the medical library. It was the feeling of the Medical Education Committee that it was necessary to have changes made to bring the school up to the stand-

ards required for an accredited two-year medical school. In 1952, the medical school was fully approved for accreditation. The four-year medical school bill was passed by the legislature in 1953 and signed by the Governor. The proceedings contain lengthy reports by the Committee on Medical Education and the Medical Center Advisory Council on the feasibility of a four-year school.

The 1 mill levy amendment to the constitution was passed at the general election November 4, 1958. The Medical Education Committee felt that money from this levy should be used for North Dakota graduates, for the two-year medical school, and to subsidize graduates of other medical schools at \$1,000 per year if they would agree to intern or practice in rural North Dakota communities. In 1956, Senate Bill 181 created a loan fund from Medical Center funds which made available loans to third- and fourth-year North Dakota resident students who were finishing medical school after transfer.

Committee reports for several years mentioned the decreasing number of qualified applicants for medical school. This is still a problem.

On the national legislation scene, many bills have been introduced relative to medical care. The Wagner-Murray-Dingell bill was presented in 1944, its proponents insisting it must be compulsory and that only government can provide for medical care. Of course, organized labor (AFL-CIO) agreed. In 1947, the Fulbright-Taft bill and the Aiken bill were introduced for creation of a Department of Health, Education and Security. The Taft-Ball-Smith bill was introduced the same year and provided for a program of grants-in-aid to states for payment of medical costs for persons unable to pay either in whole or in part for medical care, the aid being limited to those in need.

The American Medical Association in 1948 was combatting the enactment of a national compulsory health scheme. The House of Delegates of the A.M.A. voted an assessment of \$25 per member in order to defeat the enactment of such a plan.

In 1950 President Truman tried to pass his Reorganization Plan 1, which proposed the swallowing up of all medical activities in the federal government by the Federal Security Administration. The plan also proposed Oscar Ewing as F.S.A. Administrator to the post of a cabinet member or as Secretary of Welfare and Health. The plan was defeated.

The Reed-Keogh bill was introduced in Washington in 1953. No action has been taken on this bill. Recently professional incorporation acts have been passed in several states, and the Legislation Committee of the North Dakota State Medical Association is contemplating the introduction of a similar bill in the coming state legislative session.

In 1958, the Forand bill was introduced in Washington to amend the Social Security Act and Internal Revenue Code to increase the benefits payable under Federal Old Age, Survivors' and Disability Insurance program. It also would provide insurance against the costs of hospital, nursing home, and surgical services for those eligible for Old Age and Survivors' Insurance benefits. This bill was not enacted, and we now have HR 4222, the King-Anderson bill, to combat. If the King-Anderson bill is not enacted, be certain that other bills will be forthcoming.

In 1938, the secretary of the state association had this to report regarding high pressure medical health propaganda: "In their zeal to transform this world into a 100 per cent health haven, much lurid literature and

fervid oral statements keep increasing. The momentum apparently has its fountainhead in the Washington Socialist headquarters, thence spreading into various states and all local areas. Unfortunately, some of this material has a tendency to place the physician in a rather low plane."

I have reviewed briefly a few of the state association's activities in the past quarter of a century. What future problems there will be is unknown. There will be some new problems, but some that may appear new because of a new dress will, if you look underneath, have the same old foundation garment.

Speaker Christoferson thanked Dr. Boerth for his wonderful, historic farewell address, and also for a job well done this past year. He then called on Dr. E. J. Larson, president-elect, for his inaugural address.

His address follows:

I wish to thank you, Dr. Boerth. Your fine stewardship of the affairs of our society during the past year and your many years of hard work for the good of our association are deeply appreciated. I hope we may have the benefit of your experience and advice for many years to come.

In taking office as president, I do so with gratitude and humility. I am determined to carry out my duties with all the dedication at my command.

While there is turmoil throughout the medical world, and while we face many serious problems, I believe I can report that the medical situation in North Dakota is better than in some areas. We have a strong society; 466 doctors out of 505 practicing in North Dakota belong to our association. There is good spirit of cohesion and fellowship among our colleagues. Patient care is on an ever-higher plane, but there is much room for improvement.

The medical school at Grand Forks is close to the hearts of all of us. It is our school and responsibility. We should be proud of it and support it with all the moral and financial forces at our command. Dean Harwood reports that they have had a good year and have a fine class of 44 coming in the fall, all of excellent quality, and all from North Dakota with the exception of 3 from neighboring states without a medical school. He also states there is no problem in transferring at the end of the second year.

You hear much of the "grotesque public image" of the physician, and it would be interesting to probe deeply into the many reasons for it. Rather than this, I wish to go directly in search of a solution. Medicine is founded on a marriage of science to a life dedicated to service. Everyone knows this. We have known it all the time. We cannot escape it, and if we could we would not do it.

There is a great need for us to give our best to our own organization. Man is primarily effective by means of his associations with others. Without the benefits of organization, our society would resemble that of the stone age man who joined no causes, paid no dues, and served on no committees. Man's freedom is the privilege of selecting those issues he wishes to support; to participate in none is a certain way of debasing freedom.

In organized medicine the physician who thinks of himself as a rugged individualist and who opposes or refuses to take part in organizational effort is confused. Any gains or advantages achieved this way are an illusion. By means of cooperation with other physicians we have been able to bring the finest medical care to the people.

Our county, state and national associations have served

to enrich the lives of people in many ways. We can be proud of these accomplishments and be assured that quality of medical care shall remain high. Through insistence on high standards for each practicing physician, the medical profession maintains high qualifications for the protection of the patient. Our state and national societies are assisting in many ways in the upgrading of physicians.

In the field of medical education, organized Medicine has taken the lead at all times. You are all familiar with the tremendous job the A.M.A. has done to upgrade our medical schools. In the field of internship and residencies, much work has been done and invaluable information collected about opportunities for training. Standards have been set up for qualifications as specialists.

In addition to the Weekly Journal of the A.M.A., each month, 10 other specialty journals are published, plus the A.M.A. News and Today's Health. In addition to its two main meetings, much educational material is available in the form of a package library, medical films, and periodicals not widely distributed, and in many cases in a foreign language.

Organized medicine is contributing generously to promotion of education and research. We are engaged actively in the recruitment of medical students. Higher education of any form is handicapped greatly by our national tax program.

In the area of public health education, organized medicine is doing a large job with numerous publications, radio, and TV programs. A major program has been undertaken to assist in mental health research. Medicine has met its responsibility concerning threats to our national safety.

In the socioeconomic field, we have supported and promoted various plans to assist families in providing the inevitable cost of illness.

We have been alert to our responsibilities to study the effect of proposed medical care legislation. Many well-meant proposals actually might impair the quality of medical care. Other bills deserve and receive our support. More than any other profession, organized medicine has held back our nation's plunge into socialism during the past thirty years. Despite the fact that most physicians are dedicated persons who, through years of preparation and hard work, have endeavored to help mankind, we are beset by many who would destroy the physician's stature. Some, I am sure, are sincere. Others have attacked us because they fail to understand medical practice, or are ignorant of the recorded experience of medicine in other countries.

Our most vocal critics attack us because of the physician's strong opposition to their socialistic plans, proposed often for political gain. The current proposals call for a strong voice and resolute stand. I have no reservations about the validity of our position. I am concerned about the strong effort being made in high places to separate the individual physician from his association. This is the old philosophy of "divide and conquer" that has been used successfully so often. I am concerned about the apathy of many physicians when political action is required to assure continued excellence of patient care.

Too many physicians fail to take an active part in their organization and really identify themselves with the struggle which organized medicine faces to assure continued excellence of medical care. We are in a political storm; the outcome is in doubt. We must ever rebuild our temple. Let us build it upon the high spiritual mound of service; dedicated service to our patients, to our colleagues, and to our profession. Let us find unity

and cohesion in spiritual forces. Material forces are temporary. Selfishness is self-destructive. He only has begun to live who has learned to give.

A city built on a hill cannot be hidden. If we are worthy of leadership, we shall not be denied the opportunity of guiding the nation's health program in the direction of true national interest.

Dr. Boerth was then called upon to present the Fifty Year Award to Dr. John Engesather of Lakota, North Dakota.

His remarks follow:

"I would like to thank Dr. Larson for his fine words about me. I am certain that the North Dakota State Medical Association will find at the end of the year that they have made a good choice.

It is with great pleasure that I ask Dr. Toomey to escort Dr. Engesather to the speaker's rostrum.

Dr. Engesather was born September 22, 1886, in Dahlen Township, Nelson County, Dakota Territory. He was graduated with an M.D. degree from the University of Illinois on June 4, 1912, and was licensed in North Dakota in July 1914. He practiced in Brocket from 1916 to 1950 and then moved to Lakota, where he has practiced since 1950. He is a general practitioner. He served as president of the Lake Region Medical Society and chairman of the Village Board of Trustees at Brocket for 15 years and was clerk of the School District for fourteen years and a former member of the Ramsey County Planning Board.

It gives me a great deal of pleasure, Doctor, to present you with this Fifty Year Pin, and also your Certificate of Distinction.

I am sorry that my friend, Bill Long, could not be here today so I could present him with his Fifty Year Pin.

Dr. William H. Long of the Dakota Clinic, Fargo, was born July 30, 1888, at Elysian, Minnesota. He attended the University of Minnesota, graduating from there in 1912 with an M.D. degree. He was licensed in North Dakota in January 1915, and practiced in Biwabik, Minnesota, from 1912 to 1914. From 1914 to 1921 he practiced in Dickinson, North Dakota, then moved to Fargo. He is a specialist in internal medicine.

Dr. Melton, would you please come forward and receive this pin and certificate to give them to Dr. Long when you return to Fargo? Thank you."

The secretary then read the names of the nominating committee as appointed by the president, Doctor Boerth: Drs. Joe Sorkness, chairman; Frank DeCesare; and Milton Nugent.

Dr. Buckingham announced that there were 9 resolutions referred by the council to the House and that they would be presented to the Committee on Resolutions for consideration and action.

The first session of the House of Delegates adjourned at 5 p. m. to reconvene at 1:15 p. m. on Sunday, June 3, 1962. Time of adjournment was 5:00 p. m.

PROCEEDINGS Of the House of Delegates, Second Session

Speaker Christoferson called the meeting to order at 1:30 p. m. The chairman of the Credentials Committee, Dr. Countryman, reported that there was a quorum present.

Secretary Buckingham called the roll. The following delegates and alternates responded:

Drs. A. C. Burt, Fargo; G. Howard Hall, Fargo; F. M. Melton, Fargo; H. A. Norum, Fargo; D. G. Jaehning, alternate, Wahpeton; G. H. Hiltz, Cando; G. W. Seibel, New Rockford; R. C. Painter, Grand Forks; R. E. Mahowald, Grand Forks; G. L. Countryman, Grafton; W. C. Dailey, alternate, Grand Forks; C. B. Porter, alternate, Grand Forks; B. Z. Hordinsky, Drake; L. A. Giltner, Minot; G. R. Richardson, Minot; C. E. Jensen, Valley City; P. O. Dahl, Bismarck; Carl Baumgartner, Bismarck; M. A. K. Lommen, alternate, Bismarck; M. E. Nugent, Bismarck; R. B. Tudor, Bismarck; J. N. Elsworth, Jamestown; A. F. DuMais, alternate, Jamestown; Dean Strinden, Williston; N. B. Ordahl, Dickinson; W. C. Hanewald, Dickinson; R. E. Hankins, alternate, Mott; R. F. Gilliland, alternate, Dickinson; and J. M. Little, Mayville.

There were 22 delegates and 7 alternates present. Also attending the meeting were:

Drs. C. M. Lund, E. J. Larson, E. H. Boerth, W. A. Wright, F. D. Naegeli, J. D. Craven, Joe Sorkness, L. W. Larson, G. W. Toomey, Tom Pederson, C. H. Peters, G. Christianson, C. J. Glaspel, and Mr. Lyle Limond and Mr. Daniel Buchanan.

As there was no objection, the reading of the minutes of the first session was dispensed with. Dr. C. J. Glaspel of the Board of Medical Examiners was next introduced.

DR. GLASPEL: I am very happy to appear before the House of Delegates because I have always advocated a closer relationship between the Board of Medical Examiners and the House of Delegates.

I am no longer secretary, as I resigned last January. I feel it is not wise to hold a position too long. I also have a selfish reason; I wish to be away during the winter months. Also, someone younger and more vigorous could take over and do a better job than I am able to do. Any altercations I may have had with state politicians had no bearing whatsoever on my resignation.

I am sure that you realize the office of secretary has many unpleasant duties. It is he who has to inform applicants they do not meet our requirements. It is he who must inform them when they fail the examination. It is he who has to write licensed physicians in the state and tell them they are violating the Medical Practice Act when they have physicians working in their offices who are not licensed. As a result of these duties, there has been a certain amount of antagonism developed against me, as it would against anyone who tries to enforce the law.

However, any decisions I have made were made with the best interest of North Dakota Medicine at heart. Sometimes I said "No" when I wanted to say "Yes"; sometimes I said "Yes" when I should have said "No"; and sometimes I have said "Yes" or "No" when I should have said nothing. All members of the board take an oath to support the laws of the state, and in our attempt to conform with the Medical Practice Act we could not suit everyone. That is impossible.

It has been hinted that I have been rough on foreign graduates. I deny that most emphatically. I have treated them with dignity and respect. I have not been able to waive provisions of the Medical Practice Act to conform with their wishes. I believe I enjoy the good will of most of the foreign graduates in the state.

There has been criticism that the board has been lax in regard to disciplinary matters, and there might be merit to this criticism. It is our duty both to enforce discipline against our own members and against the irregulars and quacks who violate the State Medical Practice Act. I have talked for hours to licensed physicians who have been guilty of intemperance and other violations of medical ethics. It is a serious act to revoke a medical license. It is a property right, and often it is the only means a man has of earning a livelihood. Revoking a license is an unpleasant duty of the board.

I think our system of examining applicants is one of

the best in the United States. The function of the board is to determine a man's fitness to practice medicine. Is he a safe person to be responsible for sick persons? It is often very difficult to judge. I think one of the constructive factors in conducting examinations by the board is the oral examination given to each applicant by each member of the board. The moral and ethical risks involved never can be detected by written examination.

There has been some criticism of the way we handle the irregulars. I believe Minnesota has one of the best board methods in controlling irregular practitioners. However, it involves a tremendous amount of work and it takes a lot of money. What we would like, if we have knowledge of any irregular in North Dakota, is to get a patient to consult the irregular and pay him a fee, then go into court and testify against the man. That is what we need, but most patients do not wish to testify. We cannot expect much help from the state's attorneys. This is where the individual members of the component medical societies can help us a lot; in other words, convince a patient of our need for testimony against an irregular. We have some knowledge of an irregular at Underwood, but there are perhaps many in the state not known to the board. We want to do all we can, and perhaps we have not been as aggressive as we should be. However, we are limited by finances. It is a fair question for any association member to inquire of Mr. Limond what service he is receiving for his \$5.00 registration fee. I hope that, by getting help from individual members, we can do something more about the irregulars than we have done in the past.

I want to thank all the members of the House and the individual doctors in North Dakota for the fine cooperation they have given me in the years I acted on the board. There have been times in the past years when my problems and troubles have been so demanding that I considered the position impossible. But to balance this, I have had the privilege of working with the many efficient and dedicated board members in North Dakota, whose friendship I always will remember. Through the Federation of State Medical Boards of the United States, I have associated with and labored with so many capable board members from all parts of the United States, that it has been a wonderful and a delightful experience. Although my term of office will expire soon, I always will remain interested in that serious and complicated problem of medical licensure."

In order to facilitate the implementation of Resolution 6, Dr. Mahowald was called upon to present the following resolution to the House:

RESOLUTION

Whereas, the North Dakota State Medical Association is now commemorating the seventy-fifth year of medical services to the State of North Dakota, and

Whereas, the South Dakota State Medical Association has graciously joined with us in the celebration of this memorable occasion,

Be it resolved that the North Dakota State Medical Association extends greetings and sincere appreciation to the South Dakota State Medical Association for its cooperation and participation in this meeting.

Resolved that a copy of this resolution be directed to the House of Delegates of the South Dakota State Medical Association.

This resolution was adopted with the request to Mr. Limond that he present it to the House of Delegates of the South Dakota State Medical Association meeting at the Grand Pacific Hotel in Bismarck.

Since the reading of the minutes of the May 1961 sessions and the minutes of the special session of September 1961 had been dispensed with, and since all present had copies of these minutes, the chairman asked if there were any additions or corrections.

Dr. Nugent stated that he would like to have one word added to a motion he made at the special session. At that time he added an amendment to the motion that the House of Delegates instruct the Committee on Medical Economics to negotiate a schedule with the Welfare Board for MAA recipients. He asked that one word be added to this motion (p. 32 of the handbook) so that it would read "for *not* less than Plan A Blue Shield, less 10 per cent," so the Medical Economics Committee will be justified in taking this step.

This motion, as amended by Dr. Nugent, was approved and passed.

The next order of business was the report of the reference committee to consider the reports of the president, secretary, executive secretary, and treasurer.

Dr. Hanewald, chairman, presented the following reports and their discussions, which were adopted section by section and as a whole:

1. *Report of the President.* The Reference Committee commended the retiring president, Dr. Boerth, for his untiring efforts in the past year in the service of the medical profession. He also was commended for his work and time expended on the national medical scene, as well as on state medical problems, primarily negotiations with the State Welfare Board. This portion of the report was adopted.

2. *Report of the Secretary.* The Reference Committee reviewed the report and recommended that the secretaries of the district societies encourage prompt payment of annual dues. However, it questioned the use of the phrase "paid-up members" in the secretary's report, as there is no provision made for the representation of honorary members.

Speaker Christoferson called the committee's attention to Article IV, Section 4, Honorary Members, which states: "Any reputable physician who has been practicing medicine for a period of fifty years after graduation from medical school shall be eligible to honorary membership without payment of dues upon election to honorary membership by his local society, and approval by the state association through its House of Delegates."

He also cited the Bylaws, Chapter IV, Section 2, House of Delegates: "Each component society shall be entitled to send to the House of Delegates each year, one delegate for each 15 members and one for each major fraction thereof."

Speaker Christoferson added that in the committee's report it was stated that there was no provision made for the representation of honorary members. Therefore, he pointed out, in order to allow the component societies to make provision for this representation, a change in the Bylaws would be required. The committee was asked if it would like to recommend a contemplated change in the Bylaws.

The committee felt that honorary members should be given some recognition, as they can still be active in the society, even though not practicing. It suggested that some provision be made for these members. This portion of the report was adopted.

3. *Report of the Executive Secretary.* The Reference Committee reviewed the report and stated that it was concerned with the charges for rental of the auditorium and booths at the last state meeting in Fargo. It requested clarification as to future costs. This portion of the report was adopted.

4. *Report of the Treasurer.* The committee studied the several reports and statements of the Treasurer and recommended that consideration be given to transferring

lower-yielding bonds, and others, to C.D.s and other higher-yielding securities. This portion of the report was adopted.

The motion was made by Dr. Hanewald and seconded by Dr. Porter that the report be adopted as a whole.

W. C. HANEWALD, M.D., Chairman
F. M. MELTON, M.D., Vice-Chairman
C. B. PORTER, M.D., Alternate
P. O. DAHL, M.D.

Reference Committee to Consider the Reports of the Council, Councillors and Special Committees

Dr. R. C. Painter, chairman, presented the following reports and their discussions, which were adopted section by section and as a whole:

1. *Report of the Chairman of the Council.* The reference committee reviewed the report and referred the recommendation in regard to the Medic-Alert Foundation to the Resolutions Committee. The Council was commended for its untiring efforts during the past year. This portion of the report was adopted.

2. *Reports of the Councillors.* The reports of the councillors were reviewed and approved. The councillors were commended for their excellent reports. The committee also stated that it is heartening to find all districts taking an active part in legislative and political activities, as well as adopting more universally the recommended Claims Committee, Public Relations Committee, and Legislative Committee. This portion of the report was adopted.

3. *Report of the Committee on Mental Health.* This report was reviewed and approved. A recommendation relative to supporting enabling legislation which would allow the formation of community mental health service units was referred to the Resolutions Committee. This portion of the report was adopted.

4. *Report of the Committee on Cancer.* This report was reviewed and approved by the committee. The committee approves and encourages the Cancer Committee with their plans in regard to the Cancer Anti-Quackery bill to be presented to the next state legislative session. This portion of the report was adopted.

5. *Report of the Committee on Veterans Medical Service.* This report was reviewed and approved. This portion of the report was adopted.

6. *Report of the Committee on Maternal and Child Welfare.* This report was reviewed and approved. The committee also urged that the information forwarded to the committee from the State Health Officer relative to the use of poliomyelitis vaccine be transmitted by the State Health Department to all the physicians of the state and the district medical societies. This portion of the report was adopted.

7. *Report of the Committee on Diabetes.* This report was reviewed and approved. This portion of the report was adopted.

8. *Report of the Committee on Crippled Children.* This report was reviewed and approved. The Reference Committee approved their recommendation that the State Health Department undertake an educational program for physicians in the state in the PKU detection program. This portion of the report was adopted.

9. *Report of the Committee on Aging and Rehabilitation.* This report was reviewed and approved. This portion of the report was adopted.

10. *Report of the Committee on Foreign Trained*

Physicians. This report was reviewed and approved. This portion of the report was adopted.

11. *Report of the Committee on American Education Foundation.* This report was reviewed and approved. This portion of the report was adopted.

12. *Report of the Committee on School Health.* This report was reviewed and approved. This portion of the report was adopted.

13. *Report of the Committee on Pharmacy.* This report was reviewed and approved. This portion of the report was adopted.

14. *Report of the Liaison Committee to the North Dakota Bar Association.* This report was reviewed and approved. This portion of the report was adopted.

15. *Report of the Liaison Committee to the North Dakota State Dental Association.* This report was reviewed and approved. This portion of the report was adopted.

16. *Report of the Liaison Committee to the State Board of Administration.* This report was reviewed and approved. This portion of the report was adopted.

17. *Report of the Committee on Cardiovascular Diseases.* This report was reviewed and approved. This portion of the report was adopted.

18. *Report of the Committee on Emergency Medical Service.* This report was reviewed and approved. This portion of the report was adopted.

19. *Report of the Blue Cross-Blue Shield, North Dakota State Medical Association Liaison Committee.* This report was reviewed and approved. This portion of the report was adopted.

20. *Report of the Representative to the Crippled Children's Services Division of the Public Welfare Board of North Dakota.* This report was reviewed and approved. This portion of the report was adopted.

Dr. Painter moved that the report be adopted as a whole. Motion seconded by Dr. Hilts and carried.

R. C. PAINTER, M.D., Chairman
JAMES LITTLE, M.D., Vice-Chairman
G. R. RICHARDSON, M.D.
G. W. HILTS, M.D.
G. HOWARD HALL, M.D.

Reference Committee to Consider the Reports of the Delegate to the A.M.A., Medical Center Advisory Council, and Committee on Medical Education

Dr. Norum, chairman of this committee, presented the following reports and their discussions, which were adopted section by section and as a whole.

1. *Report of the Delegate to the American Medical Association.* The committee commended Dr. Wright for his faithful efforts in behalf of the American Medical Association. His report should be read by all for its concise presentation of the major problems facing medicine. Two quotations deserve repetition:

"The public airing of disagreement between large segments of medicine can only confuse and shake the confidence of the public in the medical profession, and distort the true image of medicine which the American people should have."

"Those of us who believe in the freedom of the individual and the private practice of medicine as the best way of life are continually being faced with many perplexing, unsolved problems. If our way of providing medical care is to be preserved, continuing and uneas-

ing effort must be extended by those who sincerely believe it is the better way."

This portion of the report was adopted.

2. *Report of the Representative to the Medical Center Advisory Council.* The committee reviewed and commended Dr. Woutat, representative, for a most comprehensive report. Much has been accomplished during the past year. Salient facts include the following:

1. There is assurance of a large freshman class for the fall of 1962.
2. There is \$300,000 in the Student Loan Fund.
3. The Psychiatric Training Grant program is in operation.
4. The medical school faculty has been strengthened by salary increases, improved research facilities, and the Hill research professorship.
5. The continued high level of performance depends upon the Medical Center mill levy.

The committee recommended that the Committee on Legislation watch for any attempt to change this method of financing. This portion of the report was adopted.

3. *Report of the Committee on Medical Education.* The committee reviewed the report of the Committee on Medical Education and commended Dr. Berg and his committee for their efforts and activities.

The committee approved the recommendation that students who return to North Dakota for internship and/or residency be given credit for their student loans. It also approved the recommendation that everything possible be done to increase salaries and fringe benefits for faculty members to meet the competition of other medical schools.

It was recommended that all members of the House of Delegates read the progress report by Dean Harwood. The committee does not think feasible the suggestion of postgraduate education for doctors in small towns with the aid of a traveling consultant. This portion of the report was adopted.

The motion was made by Dr. Norum and seconded by Dr. Jachning that the report be adopted as a whole.

H. A. NORUM, M.D., Chairman
B. Z. HORDINSKY, M.D.
CARL BAUMGARTNER, M.D.
G. W. SEIBEL, M.D.

Reference Committee to Consider the Reports of the Standing Committees

1. *Report of the Committee on Necrology and Medical History.* The report was reviewed and approved. Dr. Countryman, chairman, asked delegates to observe a moment of silence for departed members.

2. *Report of the Committee on Legislation.* This report was reviewed, and the committee approved the full support to AMPAC and COMPACT.

It also agreed with the recommendation of the Committee on Legislation that further study should be carried out concerning the Professional Corporate Act. The committee felt that all other interested professional groups should be invited to present their views concerning this act to the forthcoming legislature.

It was recommended that a program be set up, as has been done in the past, delegating one man in each legislative district to become the key man in that district for all purposes concerning the legislature throughout the coming session.

The committee stated that it was its hope and wish that the physicians continue to attend as many state

legislative sessions as possible. This portion of the report was adopted.

3. *Report of the Committee on Public Relations.* This report was reviewed, and the committee specifically recommended that the term Public Relations Committee be abolished and that the committee hereafter be known as the Committee on Communications. It also recommended that this committee limit its activities to the dissemination of medical information and to the relationship of the physician to the public.

It accepted the fact that the committee should be composed of a member from each of the major active committees plus any member of the society the president wishes to appoint. It was suggested that each district have a member on this committee.

It also recommended establishment of a separate committee to handle the problems of intraprofessional relationship. This committee is to be known as the Professional Ethics Committee.

This portion of the report was adopted.

The chairman then entertained a motion that the Committee on Public Relations have its name changed to Committee on Communications. The motion was made by Dr. Painter and seconded by Dr. Melton.

DR. TUDOR: I would like to know the reasons why the reference committee would like the name of this committee changed. The term "public relations" is pretty well established in the United States. Is there any specific reason for going from a "Committee on Public Relations" to a "Committee on Communications"?

SPEAKER CHRISTOFFERSON: Since changing the name of this committee would require changing the bylaws, this being defined as a "standing committee," we will have to have further consideration regarding this by the council and at the next annual session.

It was moved by Dr. Baumgartner and seconded by Dr. Tudor that this be tabled until the next annual session of the House of Delegates.

SPEAKER: It also has been recommended that a separate committee be established. The chairman would entertain a motion that the president be instructed to establish a special committee known as the Professional Ethics Committee.

DR. GILTNER: The Committee on Public Relations has to do with the physicians and the general public. If there are difficulties arising between members in the profession, this is not the business of the Public Relations Committee. I believe that a special committee should be set up to handle these problems.

SPEAKER CHRISTOFFERSON: This is being handled by the Grievance Committee of the council.

DR. TUDOR: I would like to speak more or less against

this special committee. I feel this is being taken care of by our councillors, who are men of experience in the districts. I think we have too many committees already, and by establishing this committee you would be getting men who are not as experienced as the councillors to take care of these matters. I do not feel that this committee would be necessary.

DR. GILTNER: It was our idea, in reviewing the report, that some of its subject matter did not pertain to public relations, and that a separate committee should be set up.

It was moved by Dr. Tudor and seconded by Dr. Hall that this motion regarding the separate committee be tabled. Motion passed.

4. *Report of the Official Publication Committee.* This report was reviewed, and the committee agreed that the invitation by Mr. Foster, executive secretary of the South Dakota State Medical Association, to join in a joint publication with South Dakota be considered by the House of Delegates at that time and appropriate action be taken. The committee recommended that the JOURNAL-LANCET be continued as our official publication.

It was agreed that the North Dakota State Medical Association would not be interested in entering a unilateral agreement with *Minnesota Medicine* for a regional journal unless an expression of interest had been shown by the states of Wisconsin, Iowa, South Dakota, and Nebraska. This portion of the report was adopted.

DR. NUGENT: I would like to ask for clarification of the report of the Reference Committee on Official Publication.

DR. GILTNER: We did this to fulfill the obligation of our promise to bring this before the House of Delegates.

This portion of the report was adopted.

The Chair then entertained a motion that Mr. Foster be thanked, but that the JOURNAL-LANCET will remain the official publication. This portion of the report was adopted.

5. *Report of the Committee on Public Health.* This report was reviewed, and the committee urged the Legislative Committee's action on the utilization of auto safety belts.

The increased incidence of venereal diseases in North Dakota was noted, and it was suggested that increased efforts be made in education and corrective measures on the local level for the control of these diseases. This was recommended especially for the protection of the teenage population.

G. L. COUNTRYMAN, M.D., Chairman
L. A. GILTNER, M.D.
D. C. JAEHNING, M.D., Alternate
G. W. SEIBEL, M.D.

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Book Reviews . . .

Halothane

MAX S. SADOVE, M.D., and VERNON E. WALLACE, M.D., 1962. Philadelphia: F. A. Davis. 472 pages. Illustrated. \$15.

At first glance, this volume would appear to be a reference book, containing, in general, the physics, chemistry, and pharmacology of halothane.

The equipment necessary for the use of this anesthetic is illustrated. The technique of using the agent and its clinical application and complications are presented. The remaining portion of the book contains reproductions of abstracts of the world literature on halothane.

This book will be of interest to those who are concerned with the administration of halothane.

JOHN S. LUNDY, M.D.
Chicago

Rehabilitation of Hand Function

A. N. LEONT'EV and A. V. ZAPOREZHETS, 1962. New York City: Pergamon Press. 199 pages. Illustrated. \$10.00.

A result of the experience of the Russian medical services in rehabilitating hand disabilities following World War II, this book includes many cases quoted directly from the records of that time. These are interspersed with reports of experimental work done either in Russia or by investigators elsewhere. The fact that there are more than purely mechanical disturbances involved in the loss of function following injury to the hand is emphasized.

Part I is devoted to the psychophysiologic mechanisms of restriction of function of the hand and takes up under its subheadings the relationship of movements to the character of the task, the coordination of deranged movement, the deep and gnostic sensation of the injured limb, and the problem of motor organization and restoration of movement. It emphasizes the fact that psychologic mechanisms are as important as the previously learned pattern of movement and that sensory deficits are more than just the result of loss of nerve supply but also develop because of disorganization of the patient's ability to integrate his thoughts about the extremity. These are intensified by immobilization, whether due to casts or to "dynamic immobilization" which is unconsciously carried out by the patient, to protect the injured extremity from pain during the early stages of the injury.

Part II is concerned with the process of recovery and is divided into 3 sections: first, the general course of restoration or movement; second, reorganization of the motor systems during recovery; and, third, the process of restoration of motor function. This section emphasizes the fact that general activities and training in any skill help to restore function for other skills.

The book is 199 pages long with 5 pages of references, most of them in Russian. The style is verbose and obscure. Whether this is due to the original writer or the British translator, I do not know. An example is the following taken from Part I: "The character of a movement is determined not by its own motor task and not by the original orientation of the patient's own personality but by the concrete relationship of the one to the other in

the given action." The book is printed by a photolithographic process because, according to the editors, it is so important a book that it should not be delayed by the time required to reset the manuscript by letterpress. Yet, the experimental work was apparently all done before 1945.

This is a book which will be of interest to those who are actively engaged in rehabilitation and who are, therefore, confronted with these complex problems. It is not a book for the general practitioner.

MILAND E. KNAPP, M.D.
Minneapolis

Lung Structure

STEFAN ENGEL, M.D., 1962. Springfield, Ill.: Charles C Thomas. 300 pages. Illustrated. \$15.50.

Dr. Engel provides new thought and vision in his interesting approach to the problem of lung structure. He is convinced that the physiologic and pathologic approach to disease of the lung must have a solid morphologic basis. This is also true in the field of radiology.

The author divides his work into the study of the lungs of children and then correlates the changes that occur with such diseases as bronchitis, bronchiolitis, and bronchiectasis. He attempts to determine the variations in the structure of the lung at various ages and emphasizes the importance of bronchomalacia in the development of further pulmonary problems. By bronchomalacia, he means that infiltration of long duration, accompanied by a slight bronchial dilation, leads to degeneration of the bronchial walls. This, then, leads into a chronic form of bronchiectasis. Dr. Engel also discusses the evolution of the lung and reviews the comparative anatomy of the respiratory tissues; he presents his thoughts concerning pneumonia and other pulmonary conditions.

The book is well written, the format is excellent, and the illustrations are adequate. His comments are certainly challenging, and many will find them difficult to accept. He foresaw this, for he comments that his conclusions are the result of long, personal investigation into the lung structure. The book has a limited appeal because of its nature but certainly warrants reading by anyone interested in pulmonary disease and pulmonary physiology.

JOHN F. BRIGGS, M.D.
St. Paul

Psychoanalysis of Behavior:

The Collected Papers of Sandor Rado

SANDOR RADO, M.D., Ph.D., volume 2, 1962. New York: Grune & Stratton. 196 pages. Illustrated. \$6.50.

A collection of all of the papers published between 1956 and 1961 has been made by Dr. Rado. Some of them overlap considerably, and the only central organization is the multifaceted Dr. Rado himself. If the reader wishes a view of Dr. Rado, around 1958, the book is to be recommended. Certainly Dr. Rado is always readable, often enlightening, and never dull. Some of his charm is due to the tendency to state controversial theories as strongly as though they were universally accepted.

(Continued on page 18A)

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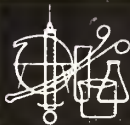
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BOOK REVIEWS

(Continued from page 16A)

This, however, makes the book of little interest to the nontechnical reader.

The first paper in this series describes the promising beginnings of a controlled clinical study of schizophrenia, the pilot studies of which were completed in 1955. Unfortunately, the "... complete report on these phases of our material ..." is not to be found among the subsequent 18 papers published through 1961. The others include clinical papers, addresses, discussions of papers, and notes on teaching.

Dr. Rado's somewhat unorthodox views are well presented throughout the book. For example, the analysis of the transference neurosis is a mainstay of classical psychoanalysis. Patients always bring the doctor a set of ready-made expectations and emotional reactions—transferences from previous emotional experiences. The neurotic, of course, transfers his neurotic patterns to his relationship with the doctor. Classical analysis sees this as a useful model. Once the transference neurosis is resolved, some generalization to other life experiences may be expected. This concept is not unique to psychoanalysis and is implicit in such concepts as "corrective emotional experience" and "resolution of parataxic distortions"—concepts that come from outside classic psychoanalysis.

Observe, though, how Dr. Rado deals with the analysis of the transference neurosis: "At the end of such phases the patient was shown by the usual technique of historical interpretation that the true object of his rage was his father rather than the physician. This cumbersome procedure did less for the patient than did Breuer's hypnecatharsis in which the released rage retained its original object. Only Freud's preoccupation with the (erroneous) idea that this scapegoat technique would allow him to explore otherwise inaccessible phases of the patient's past could have persuaded him to consider it an effective therapeutic measure."

Although this book cannot be recommended as an introduction to current psychoanalytic theory, the reader with even moderate sophistication about psychoanalytic concepts will find the idiosyncratic portions of Rado's theorizing immediately apparent. Such a reader will be rewarded with an occasional well-phrased psychodynamic observation, while the more iconoclastic sections will, at the very least, be stimulating and thought provoking.

ENOCII CALLAWAY III, M.D.
San Francisco

NEW BOOKS RECEIVED

Books and publications received will be listed here periodically, and such mention must be regarded as sufficient return for the courtesy of the sender. Books of special interest to our readers will be reviewed as space permits.

Elements of Progressive Patient Care. Public Health Service Publication No. 930-C-1, 1962. Washington, D. C., U. S. Government Printing Office. 65 pages. Illustrated. 45 cents.

Essentials of Pediatric Psychiatry. RUBEN MEYER, MORTON LEVITT, MORDECAI L. FALICK, and BEN O. RUBENSTEIN, 1962. New York: Appleton-Century-Crofts. 208 pages. Illustrated. \$6.00.

Enzymes and Drug Action. J. L. MONGAR and A. V. S. DE REUCK, Editors, 1962. Boston: Little, Brown & Co. 556 pages. Illustrated. \$12.50.



